(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 443 568 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
12.06.1996 Bulletin 1996/24

(21) Application number: **91102513.8**

(22) Date of filing: **21.02.1991**

(51) Int. Cl.[6]: **C07D 495/04**, A61K 31/435 // (C07D495/04, 333:00, 221:00), (C07D495/04, 333:00, 239:00)

(54) Fused thiophene derivatives, their production and use

Annelierte Thiophen-Derivate, ihre Herstellung und Verwendung

Dérivés fusés de thiophène, leur préparation et leur application

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: **22.02.1990 JP 42125/90**
17.01.1991 JP 3958/91

(43) Date of publication of application:
28.08.1991 Bulletin 1991/35

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Description

FIELD OF THE INVENTION

The present invention relates to novel fused thiophene derivatives having potent pharmacological activity and intermediates for the preparation thereof. More particularly, the present invention relates to compounds having potent angiotensin II antagonist activity and antihypertensive activity, which are useful as therapeutic agents for treating circulatory diseases such as hypertensive diseases, heart diseases, strokes, etc.

BACKGROUND OF THE INVENTION

The renin-angiotensin system is involved in the homeostatic function to control systemic blood pressure, the volume of body fluid, balance among the electrolytes, etc., associated with the aldosterone system. Development of angiotensin II converting enzyme inhibitors (ACE inhibitor) (this converting enzyme produces angiotensin II which possesses strong vasoconstrictive activity) has clarified the relation between the renin-angiotensin system and hypertension. Since angiotensin II elevates blood pressure via the angiotensin II receptors on cell membranes, angiotensin II antagonists as well as the ACE inhibitor would be useful in treating hypertension.

It has been reported that various angiotensin II analogues such as saralasin, [Sar^1,Ile^8]A II, and the like, possess potent angiotensin II antagonist activity.

It has, however, been reported that, when peptide antagonists are administered parenterally, their actions are not prolonged and, when administered orally, they are ineffective (M. A. Ondetti and D. W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

Non-peptide angiotensin II antagonists are disclosed in Japanese Patent Laid Open No. 71073/1981; No. 71074/1981; No. 92270/1982; No. 157768/1983; No. 240683/1987; No. 23868/1988; and No. 117876/1989, and European Patent Laid Open No. 0323841, etc.

Imidazole derivatives having angiotensin II antagonist activity are disclosed in A. T. Chiu et al., Eur. J. Pharm., 157, 13 (1981), P. C. Wong et al., J. Pharmcol. Exp. Ther., 247, 1 (1988), P. C. Wong et al. ,Hypertension, 13, 489 (1989), etc.

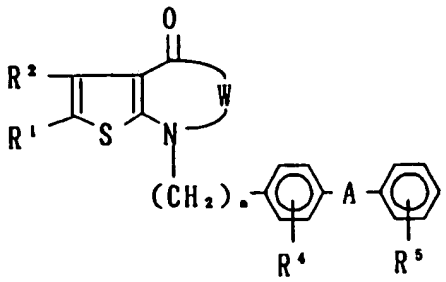
US 4,670,560 discloses thienopyrimidine-2,4-dione derivatives as vasodilating agents and anti-hypertensive agents. US 4,835,157 discloses thienopyrimidine-2,4-dione piperidine derivatives as selective serotonin antagonists and alpha adrenergic blocking agents. Substituted benzimidazoles as angiotensin II antagonists are disclosed in EP-A-0 400 835.

It has not yet been known that fused thiophene derivatives possess potent angiotensin II antagonist activity.

SUMMARY OF THE INVENTION

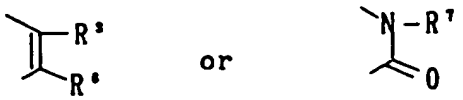
The present inventors made extensive investigations to prepare useful compounds which have angiotensin II antagonist activity. As a result of these researches, the present inventors have succeeded in synthesizing fused thiophene derivatives possessing excellently potent angiotensin II antagonist activity and developed their work to accomplish the present invention.

The present invention provides fused thiophene derivatives having the formula I:



(I)

wherein W is



R^1 and R^2 which may be the same or different, are each independently

(1) hydrogen,
(2) halogen,
(3) cyano,
(4) nitro,
(5) a group having the formula: R^8CONH- wherein R^8 is hydrogen or (C_{1-8})alkyl group which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or naphthyl, or
(6) a hydrocarbon residue selected from the group consisting of (i) (C_{1-8})alkyl, (ii) (C_{2-8})alkenyl, (iii) (C_{2-8})alkynyl, (iv) (C_{3-8})cycloalkyl, (v) an aromatic hydrocarbon selected from the group consisting of phenyl and naphthyl, wherein said hydrocarbon residue may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;

R^3 is

(1) hydrogen,
(2) (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino, or
(3) -COD wherein D is hydrogen, C_{1-4}-alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino, wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro or lower (C_{1-4}) alkoxy;

R^4 is hydrogen, halogen or nitro;
R^5 is carboxyl, lower (C_{1-4})alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;
R^6 is hydrogen or (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;
R^7 is a hydrocarbon residue which may be substituted like R^1 and R^2; A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group selected from the group consisting of (C_{1-4})alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2-, or -CH=CH-; and n is an integer of 1 or 2;
and a pharmaceutically acceptable salt thereof.

These compounds are potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the fused thiophene derivative having the formula I and a pharmaceutically acceptable carrier useful in treating circulatory

system diseases such as hypertensive diseases, heart diseases, strokes, etc., and processes for preparing such compounds and compositions.

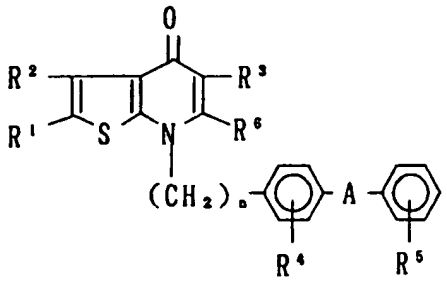
Still another aspect of the present invention relates to a use of the fused thiophene derivative having the formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides fused thiophene derivatives having the formula I and the pharmaceutically acceptable salts thereof, which possess potent angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive diseases, heart diseases, strokes, etc., pharmaceutical compositions comprising an effective amount of the fused thiophene derivative having the formula I and a pharmaceutically acceptable carrier useful in treating said circulatory diseases and processes for preparing such compounds and compositions.

The present invention further provides a method for treating said circulatory system diseases of hosts, which comprises administering an effective amount of the fused thiophene derivative having the formula I or the pharmaceutical composition thereof to said host.

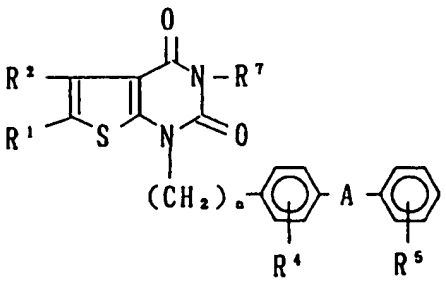
An important group of compounds according to the present invention are the compounds of the formula Ia:



(Ia)

wherein R^1 and R^2 are as defined above;
R^3 is hydrogen, formyl, optionally substituted alkyl or alkenyl as defined in claim 1, or -COD wherein D is alkoxy, hydroxy, halogen, or optionally substituted amino as defined above;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined above;
R^6, A and n are as defined above
and a pharmaceutically acceptable salt thereof.

Another important group of compounds according to the present invention are the compounds of the formula Ib:



(Ib)

wherein R^1 and R^2 are as defined above;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined above;
R^7, A and n are as defined above;
and a pharmaceutically acceptable salt thereof.

With regard to the foregoing formula (I), halogen for R^1 and R^2 include fluorine, chlorine, bromine, and iodine.

R^1 and R^2 include a group having the formula: R^8CONH- wherein R^8 is hydrogen or lower alkyl of 1 to 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like), which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or naphthyl.

Examples of hydrocarbon residues for R^1, R^2 and R^7 include acyclic hydrocarbon residues such as lower alkyl of 1 to 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like), lower alkenyl of 2 to 8 carbon atoms (e.g. vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like), and lower alkynyl of 2 to 8 carbon atoms (e.g. ethynyl, 2-butynyl, 2-pentynyl, 2-octynyl, and the like); cyclic hydrocarbon residues such as alicyclic hydrocarbon residues of 3 to 8 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, cyclooctyl and the like), and aromatic hydrocarbon residues selected from the group consisting of phenyl and naphthyl.

Said hydrocarbon residues for R^1, R^2 and R^7 may be optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), lower (C_{1-4}) alkyl (e.g. methyl, ethyl, and the like), halogen (e.g. F, Cl, Br and the like), nitro, amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxyphenyl)piperazino, lower (C_{1-4}) alkanoyloxy, benzoyloxy, phenyl which may be optionally substituted with halogen, nitro, lower (C_{1-4}) alkoxy or lower (C_{1-4}) alkyl at an optional position on the phenyl ring , or a group having the formula: -COD' wherein D' is hydroxy, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino or N-phenylpiperazino.

Alkyl or alkenyl groups for R^3 and R^6 are lower alkyl of 1 to 8 carbon atoms and lower alkenyl of 2 to 8 carbon atoms which may be straight or branched. Examples of such alkyl and alkenyl groups for R^3 and R^6 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like. Said alkyl or alkenyl groups for R^3 may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), halogen, lower (C_{1-4}) alkoxy (e.g. methoxyl, ethoxyl, and the like) and -COD" wherein D" is lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), hydroxy, halogen, amino, N-lower (C_{1-4}) alkyl amino such as methylamino and ethylamino, N,N-dilower (C_{1-4}) alkyl amino such as dimethylamino and diethylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino and N-phenylpiperazino.

Said alkyl or alkenyl groups for R^6 may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), halogen, lower (C_{1-4}) alkoxy (e.g. methoxyl, ethoxyl, and the like) and -COD" wherein D" is lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), hydroxy, halogen, N-lower (C_{1-4}) alkyl amino such as methylamino and ethylamino, N,N-dilower (C_{1-4}) alkyl amino such as dimethylamino and diethylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino and N-phenylpiperazino. Where R^3 is a group having the formula: -COD, alkoxy groups for D include lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like). For D, examples of halogen include Cl, Br and the like. D may further represent amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, and the like), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, and the like), phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino or N-(p-fluorophenyl)piperazino, wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, and the like), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, and the like), morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro, or lower (C_{1-4}) alkoxy (e.g. methoxyl, ethoxyl).

The compounds wherein D is halogen are useful as synthetic intermediates for the preparation of those wherein D is alkoxy.

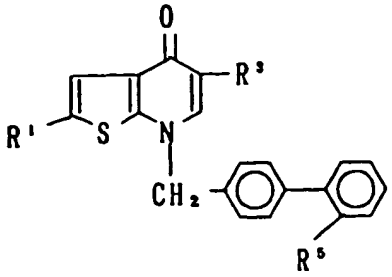
R^4 represents hydrogen, halogen (e.g. chlorine, bromine, and the like) or nitro, which may be in the ortho or meta position to the -A- group.

The residues capable of forming an anion and residues convertible into the anion for R^5 are carboxyl, lower (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide (-$NHSO_2CF_3$), phosphoric acid or sulfonic acid. Such residues include those which are capable of forming anions either chemically or under biological and/or physiological conditions. R^5 is preferable in the ortho position. The compounds wherein R^5 is a residue capable of forming an anion or convertible thereinto chemically (e.g. by oxidation, reduction or hydrolysis) (e.g. cyano and the like), are useful as synthetic intermediates.

A shows that the adjacent phenylene group is bonded to the phenyl group directly or through a spacer whose atomic chain is 2 or less.

Such spacers are lower (C_{1-4}) alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2-, -CH=CH-.

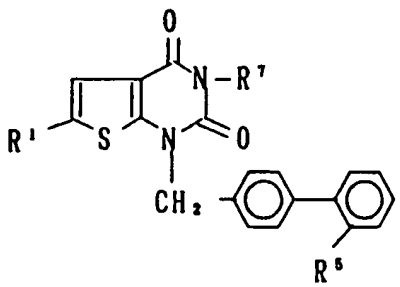
A preferred embodiment of the invention is a compound of the formula (Ia'):



(Ia')

wherein R^1 is (C_{1-8}) alkyl; R^3 is hydrogen, (C_{1-8})alkyl which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy or -COD" wherein D" is (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino (e.g. lower (C_{1-4}) alkoxylmethyl, and the like) or -COD wherein D is hydrogen, (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino; and R^5 is carboxyl or tetrazolyl (inter alia tetrazolyl); and the pharmaceutically acceptable salts thereof.

A further preferred embodiment of the invention is a compound of the formula (Ib').

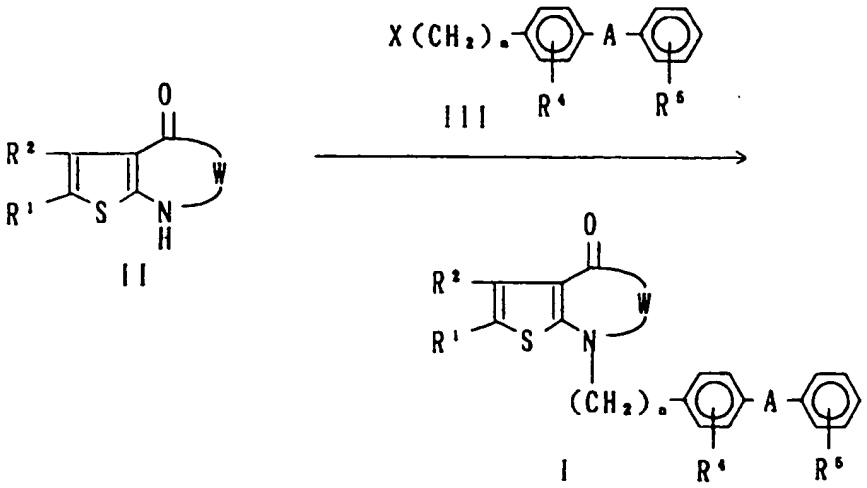


(Ib')

wherein R^1 is (C_{1-8})alkyl; R^7 is (C_{1-8})alkyl which may be optionally substituted with phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, or -COD' wherein D' is (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino or N-phenylpiperazino, (C_{3-8})cycloalkyl, or phenyl or naphthyl which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino; and R^5 is carboxyl or tetrazolyl (inter alia tetrazolyl); and the pharmaceutically acceptable salts thereof.

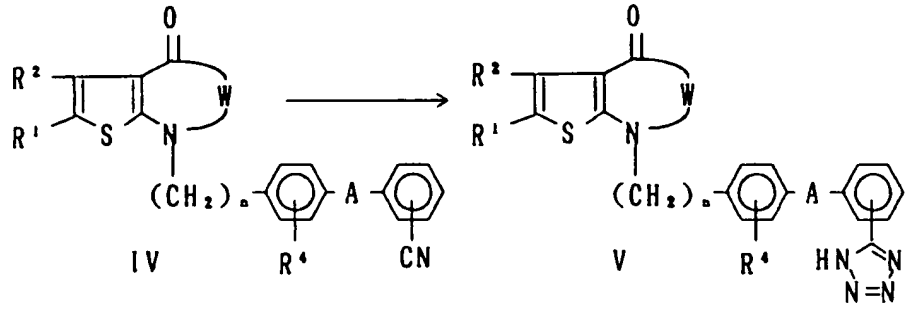
The compounds (I) of the present invention may be prepared by several reaction schemes, as illustrated below for a preferred compound.

Scheme A



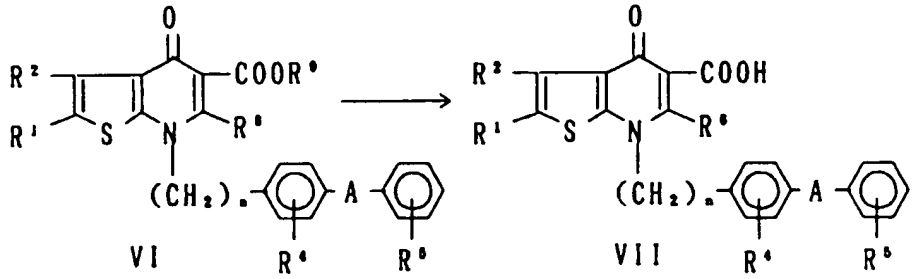
wherein R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, and X is halogen.

Scheme B



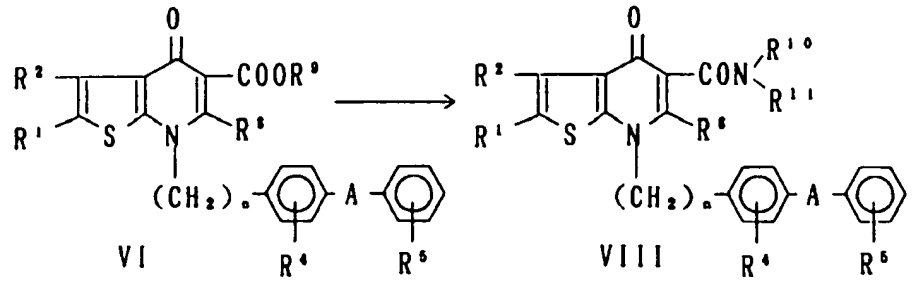
wherein each group is of the same meaning as defined above.

Scheme C



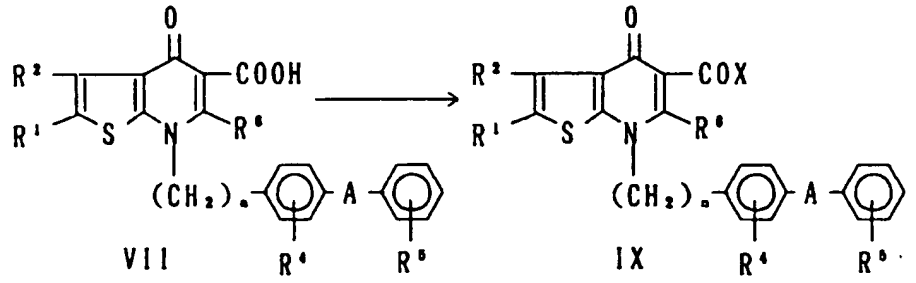
wherein R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and R^9 is lower (C_{1-4}) alkyl.

Scheme D



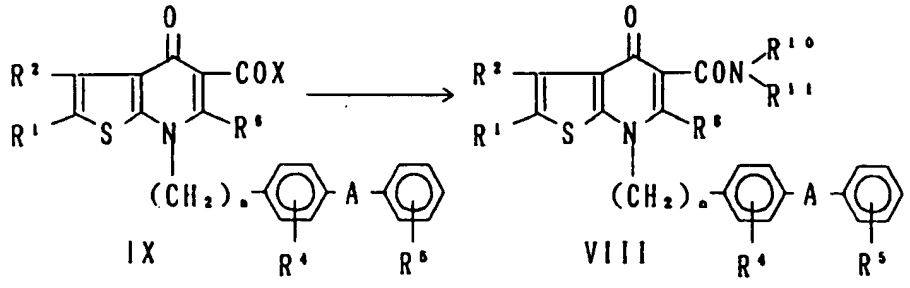
wherein R^1, R^2, R^4, R^5, R^6, R^9, A and n have the above-defined meanings, and R^{10} and R^{11} are each independently hydrogen or a hydrocarbon residue.

Scheme E



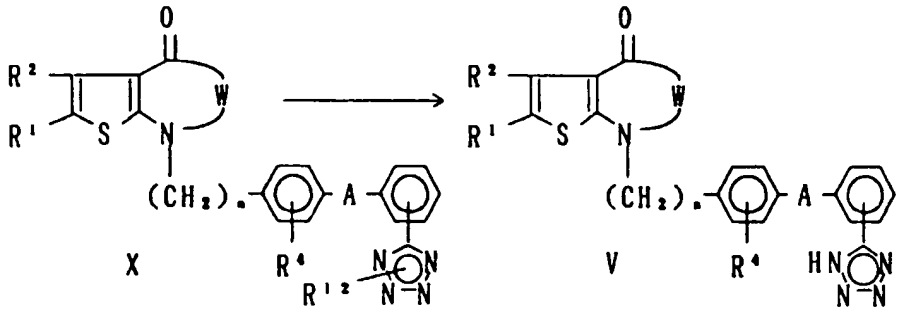
wherein R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and X is halogen.

Scheme F



wherein R^1, R^2, R^4, R^5, R^6, R^{10}, R^{11}, X, A and n have the above-defined meanings.

Scheme G



wherein R^1, R^2, R^4, A, W and n have the above-defined meanings and R^{12} is a protective group.

The reaction as illustrated in Scheme A is an alkylation using an alkylating agent in the presence of a base. One molar portion of the compound (II) is employed with 1 to 3 moles of the base and about 1 to about 3 moles of the alkylating agent. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, acetone, ethylmethylketone, and the like. Examples of such bases include sodium hydride, potassium t-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, and the like. Examples of such alkylating agents include substituted halides (e.g. chlorides, bromides, iodides, and the like), substituted sulfonate esters (e.g. methyl p-toluenesulfonate esters, and the like), etc.

The reaction conditions may vary depending on the combination of the base and the alkylating agent. A temperature in the range of ice-cooling - 100°C is preferred and a reaction period of 1-about 10 hours is preferably employed.

The cyano substituent on the benzene of the compounds (IV) is reacted with various azides to form the tetrazole compounds (V) as illustrated in Scheme B. One molar portion of the compound (IV) is employed with 1-10 moles of the azide. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, toluene, benzene, and the like.

Examples of such azides include trialkyl-tin azide, triphenyl-tin azide, hydrogen azide, and the like. In the case where the organo-tin azide compound is employed, the reaction is carried out in toluene or benzene by heating under reflux for a period of 10 - 30 hours. When the hydrogen azide is used, 5 moles of sodium azide and ammonium chloride per compound (IV) are employed and the reaction is conducted in dimethylformamide at a temperature ranging from 100°C - 130°C for 1-10 days. During this reaction, it is preferable to facilitate working by adding an appropriate amount of sodium azide and ammonium chloride.

The reaction as illustrated in Scheme C is hydrolysis of the ester (VI) into the carboxylic acid (VII) in the presence of an alkali. One molar portion of the compound (VI) is employed with 1 to 3 moles of the alkali. The reaction is conven-

tionally conducted in solvents such as alcohols containing water (e.g. methanol, ethanol, methylcellosolve, and the like). Examples of such alkalis include sodium hydroxide, potassium hydroxide, and the like. The reaction is preferably conducted at a temperature in the range of room temperature - 100°C for 1-10 hours.

The compounds (VI) are reacted with various amines to form the amide compounds (VIII) as illustrated in Scheme D. One molar portion of the compound (VI) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) or without a solvent. The reaction is preferably conducted at a temperature in the range of room temperature - 200°C. Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, o-methoxybenzylamine, etc.), arylamines (e.g. aniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, etc.), and the like.

The compounds (VII) are treated with various halogenating agents to form the acid halides (IX) as illustrated in Scheme E. One molar portion of the compound (VII) is employed with about 1 to 5 moles of the halogenating agent. The reaction is conventionally conducted in solvents such as halogenated hydrocarbons (e.g. $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, and the like), ethers (e.g. tetrahydrofuran, dioxane, and the like) and aromatic hydrocarbons (e.g. benzene, toluene, and the like). Examples of such halogenating agents include oxalyl chloride, thionyl chloride, phosphorous oxychloride, phosphorous trichloride, phosphorous pentachloride, etc. The reaction is preferably conducted at room temperature - 100°C for 1-10 hours.

The acid halides (IX) are reacted with various amines to form the amide compounds (VIII) as illustrated in Scheme F. One molar portion of the compound (IX) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) and ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, and the like). Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, o-methoxybenzylamine, etc.), arylamines (e.g. aniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, etc.), and the like.

The protective group (R^{12}) on the tetrazole compound (X) leaves to form the tetrazole compound (V) as illustrated in Scheme G. Reaction conditions may vary depending on the protective group (R^{12}) used. When R^{12} is triphenylmethyl (trityl), 2-tetrahydropyranyl, methoxymethyl, ethoxymethyl, or the like, the leaving of the protective group is conveniently conducted in aqueous alcohols (e.g. methanol, ethanol, etc) containing from about 0.5N to about 2N hydrochloric acid or acetic acid, or in a mixture of trifluoroacetic acid and water (1:2 ~5) at room temperature for 1-10 hours.

The compounds (I) thus produced via the reaction processes as depicted in Schemes A, B, C, D, E, F and G can be isolated and purified from the reaction mixture according to conventional methods such as, for example, evaporation of solvents, extraction by water or organic solvents, concentration, neutralization, recrystallization, distillation, column chromatography and the like, to obtain a crystalline or oily product.

The compounds (I) of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

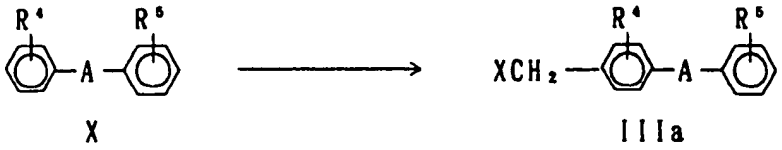
The starting materials (II) can be easily prepared by or according to the known techniques, for example, as disclosed in:

(1) P. Blaszkiewicz, H. Vorbruggen and H. J. Kesler (Schering AG): DOS 2, 447,477 (15. 4. 76); Chem. Abst., 85, 46627 (1976),
(2) Y. Kuwada, K. Meguro, Y. Sato and T. Fugono (Takeda Chem.): DOS 2, 435,025 (6. 25. 75); Chem. Abst., 82, 156252 (1975), etc.

Among the starting materials (III), the compounds wherein n is 1 (the compounds (IIIa)) is prepared by the known techniques as disclosed in Japanese Patent Laid Open No. 23868/1988; and No. 117876/1989, and European Patent Laid Open No. 0323841.

As illustrated in Scheme H, the compounds (IIIa) can also be easily prepared by halogenomethylation of the compounds (X) commercially available or easily prepared according to methods described in known literatures such as, for example, A. A. Vansheidt et al., Khim. Nauka i Prom., 2, 799 (1957),

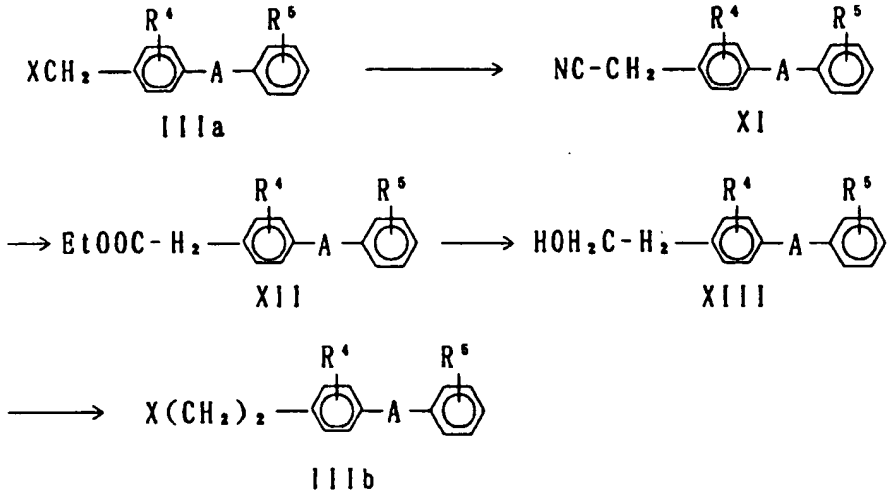
Scheme H



wherein each group has the above-defined meaning.

The compound (III) wherein n is 2 (the compounds (IIIb)) can be prepared from the compounds (IIIa) according to the methods as illustrated in Scheme I.

Scheme I



wherein each group has the above-defined meaning.

The compounds (I) and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, rabbits, rats, etc.). Further, the compounds (I) and salts thereof according to the present invention are of quite low toxicity and useful in treating not only hypertension but also circulatory system diseases such as heart diseases, strokes and the like.

For therapeutic use, the compounds (I) and salts thereof can be administered as pharmaceutical compositions (e.g, powders, granules, tablets, pills, capsules, injections, solutions and the like) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. When used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, selected from the range of about 10 mg to 100 mg a day orally and from the range of about 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention.

Example

The invention is further illustrated but in no way limited by the following reference examples, working examples, pharmaceutical examples and experimental examples.

In the specification of the present application, examples of the abbreviations used are given below. Me: Methyl, Et: Ethyl, Pr: Propyl, Bu: Butyl, iBu: Isobutyl, tBu: Tert-butyl, Ph: Phenyl, DMF: Dimethylformamide.

Reference Example 1

Isobutyl 2-ethyl-4-hydroxythieno[2,3-b]-pyridine-5-carboxylate

A mixture of 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylic acid (200 mg, 0.9 mmol) and boron trifluoride-ethyl ether (47 %, 0.5 ml) in isobutyl alcohol (10ml) was heated under reflux for 5 hours. The reaction mixture was allowed to cool and concentrated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/ethyl acetate (3:1) to give 80 mg (31 %) of the title compound as colorless crystals.
m.p. 156-158 °C.
IR (KBr)cm^{-1}: 1700, 1595, 1520.

NMR ($CDCl_3$) δ : 1.05(6H, d, J=6.6Hz), 1.40(3H, t, J=7.4Hz), 2.0-2.2(1H, m), 2.94(2H, q, J=7.4, 15.0Hz), 4.20(2H, d, J=6.6Hz), 7.16(1H, s), 8.84(1H, s).

Elemental Analysis for $C_{14}H_{17}NO_3 \cdot H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 63.38;	H, 5.70;	N, 15.84
Found:	C, 63.70;	H, 5.44;	N, 15.50.

Reference Example 2

2-Methoxyethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate

A mixture of 2-ethyl-4-hydroxythieno[2,3-b)pyridine-5-carboxylic acid (380 mg, 1.7 mmol) and DMF (0.13 ml, 1.7 mmol)in benzene (5 ml) was heated to 60 °C and to the reaction mixture was added thionyl chloride (0.15 ml, 2.1 mmol). The mixture was stirred at 60 °C for 3 hours and then allowed to cool with an ice bath. The precipitated product was collected by filtration and washed with benzene. The resulting precipitate (223 mg) was dissolved in a mixture of 2-methoxyethanol (0.3 ml) and CH_2Cl_2 (5 ml) and then triethyamine (0.7 ml) were added to the solution. The mixture was stirred for 30 minutes and poured into chloroform. The resulting mixture was washed with 1N hydrochloric acid, dried ($MgSO_4$) and evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/hexane/chloroform (1:1:1) and then chloroform/methanol (9:1) to give 200 mg (41 %) of the title compound as colorless powders.
IR (KBr)cm^{-1}: 1700, 1590, 1530, 1480.

NMR ($CDCl_3$) δ : 1.39(3H, t, J=7.4Hz), 2.94(2H, q, J=7.4, 15.0Hz), 3.45(3H, s), 3.7-3.8(2H, m), 4.5-4.6(2H, m), 7.17(1H, s), 8.87(1H, s).

Elemental Analysis for $C_{13}H_{15}NO_4S$			
	C (%)	H (%)	N (%)
Calcd:	C, 55.50;	H, 5.37;	N, 4.98
Found:	C, 55.47;	H, 5.38;	N, 4.95

Reference Example 3

Ethyl 2-ethyl-4-hydroxy-3-nitrothieno[2,3-b]pyridine-5-carboxylate

A solution of ethyl 2-ethyl-4-hydroxythieno-[2,3-b]pyridine-5-carboxylate (1.0 g, 4.0 mmol) in conc. sulfuric acid (10 ml) was cooled to -5 °C and a solution of sodium nitrate (370 mg, 4.3 mmol) in conc. sulfuric acid (5 ml) was added dropwise to the chilled solution. The reaction mixture was stirred at -3 °C - -5 °C for 1 hour and poured into ice-water. The precipitated product was collected by filtration and washed with cold water and then ethanol. The resulting precipitate was dissolved in chloroform, washed with a saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated in vacuo. The resulting yellow solid was washed with a mixture of ether/hexane, and dried to give 960 mg (81 %) of the title compound. m.p. 194-201 °C (dec.).
IR (KBr)cm^{-1}: 1700, 1600, 1590, 1530.

NMR ($CDCl_3$) δ : 1.42(3H, t, J=7.4Hz), 1.47(3H, t, J=7.2Hz), 3.05(2H, q, J=7.4, 15.0Hz), 4.50(2H, q, J=7.2, 14.4Hz), 8.93(1H, s).

Elemental Analysis for $C_{12}H_{12}N_2O_5S$			
	C (%)	H (%)	N (%)
Calcd:	C, 48.64;	H, 4.08;	N, 9.45
Found:	C, 48.48;	H, 4.01;	N, 9.28

Reference Example 4

Ethyl 2-ethyl-7-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

To a solution of ethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (1.00 g, 4 mmol) in 20 ml of DMF) was added sodium hydride (60 % dispersion in oil, 160 mg) and the mixture was stirred for 10 minutes. To the reaction mixture was added 4-[2'-(N-trityltetrazol-5-yl)phenyl]benzyl bromide (2.23 g, 4 mmol) and the mixture was heated at 90 °C for 1 hour with stirring. The reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/dichloromethane (1:1) to give 2.24 g (77 %) of the title compound as white crystals. m.p. 195-198 °C.
IR (KBr)cm^{-1}: 1730, 1705, 1620.

NMR ($CDCl_3$) δ : 1.27(3H, t, J=9.6Hz), 1.39(3H, t, J=6.8Hz), 2.72(2H, q, J=8.9, 15.0Hz), 4.38(2H, q, J=7.2, 13.8Hz), 5.02(2H, s), 6.80-8.0(9H, m), 8.29(1H, s).

Elemental Analysis for $C_{45}H_{37}N_5O_3S$			
	C (%)	H (%)	N (%)
Calcd:	C, 74.26;	H, 5.12;	N, 9.62
Found:	C, 74.09;	H, 5.18;	N, 9.50

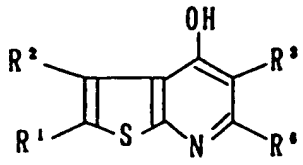
The following compounds (II) can be easily prepared by or according to the known techniques, for example, as disclosed in:

(1) P. Blaszkiewicz, H. Vorbruggen and H. J. Kesler (Schering AG): DOS 2, 447,477 (15. 4. 76); Chem. Abst., 85, 46627 (1976),
(2) Y. Kuwada, K. Meguro, Y. Sato and T. Fugono (Takeda Chem.): DOS 2, 435,025 (6. 25. 75); Chem. Abst., 82, 156252 (1975),
(3) R. K. Russell, J. B. Press, R. A. Rampulla, J. J. McNally, R. Falotico, J. A. Keiser, D. A. Bright and A. Tobia, J. Med. Chem., 31, 1786 (1988),
(4) M. Suwada, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi and H. Fuumi, Chem. Pharm. Bull., 37, 2091 (1989),

(5) M. Sugiyama, T. Sakamoto, K. Tabata and H. Fuumi, Chem. Pharm. Bull., 37, 2717 (1989),
(6) G. D. Madding and M. D. Thompson, J. Heterocyclic Chem., 24, 581 (1987),
(7) J. Barker, P. R. Huddleston and D. Holmes, J. Chem. Research (S), 1985, 214,
(8) J. Barker, P. R. Huddleston and D. Holmes, J. Chem. Research (S), 1986, 122,
(9) M. A. Khan and A. E. Guarconi, J. Heterocyclic Chem., 14, 807 (1977),
(10) K. Ogawa, I. Yamawaki, Y. Matsusita, N. Nomura and I. Okazaki, WO 89/02432.

The compounds (III) can alternatively be prepared in the same manner as described in Reference Example 1, 2, or 3.

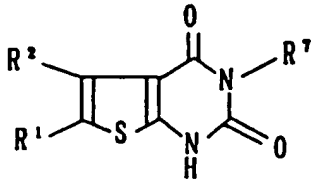
TABLE 1



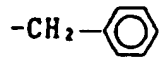
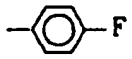
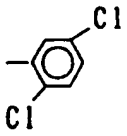
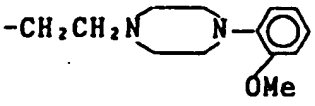
(II)

Reference Example No.	R^1	R^2	R^3	R^6	mp (°C)
5-1	Br	H	COOEt	H	208-209
5-2	H	H	COOEt	H	105-108
6	Me	H	COOEt	H	122-124
7	Pr	H	COOEt	H	74- 75
8	Et	H	$COOCH_2CH_2OMe$	H	powder
9	Et	H	CH_2OH	H	> 260 (decomp.)

TABLE 2

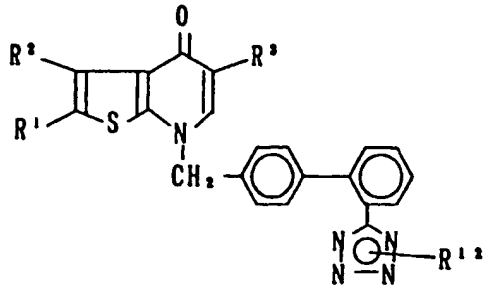


(II)

Reference Example No.	R^1	R^2	R^7	mp (°C)
10	Et	H	Bu	217-220
11	Et	H		259-262
12	Et	H	Et	243-244
13	Et	H		>290
14	Et	H		268-275
15	Et	H		285-288
16	Et	H	$-CH_2COOEt$	201-204
17	Et	H		239-241

The following compounds (Reference Examples 18-32) were prepared in the same manner as in Reference Example 4.

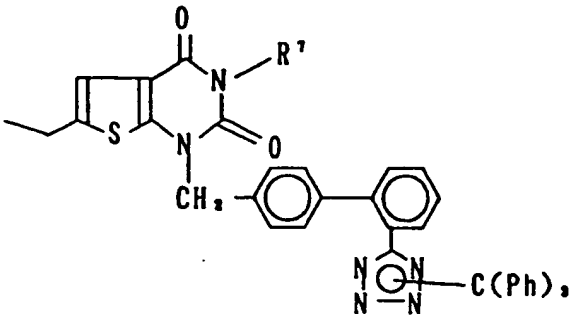
TABLE 3



Reference Example No.	R^1	R^2	R^3	R^{12}	Yield (%)	mp (°C)
18	Et	H	$-COOCH_2CH_2OCH_3$	-C(Ph)$_3$	30	192-198
19	Et	H	-COOiBu	-C(Ph)$_3$	40	209-212
20	Et	NO_2	-COOEt	-C(Ph)$_3$	34	
21	Me	H	-COOEt	-C(Ph)$_3$	53	205-207
22	Pr	H	-COOEt	-C(Ph)$_3$	51	181-187
23	Br	H	-COOEt	-C(Ph)$_3$	47	129-133
24	H	H	-COOEt	-C(Ph)$_3$	50	137-139
25	Et	H	$-CH_2OH$	-C(Ph)$_3$	46	powder
26	Et	H	H	-C(Ph)$_3$	46	
27	Et	H	-CHO	-C(Ph)$_3$	67	150-156
28	Et	H	-CH=CH-COOtBu	-C(Ph)$_3$	56	powder
29	Et	H	-COOEt	-COOtBu	62	
30	CN	H	-COOEt	-C(Ph)$_3$	21	129-131
31	Et	H	$-CONCH_2Ph$ CH_3	-C(Ph)$_3$	56	169-171
32	Et	H	$-CH_2OMe$	-C(Ph)$_3$	26	powder

The following compounds (Reference Examples 33-40) were prepared in the same manner as in Reference Example 4.

TABLE 4a



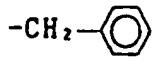
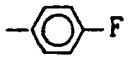
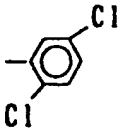
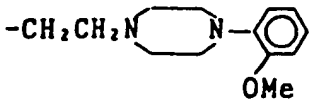
Reference Example No.	R^7	mp (°C)	Yield (%)
33	Bu	173-176	57
34		204-207	47
35	Et	117-122	57
36		192-193	67
37		193-197	79
38		141-144	48
39	$-CH_2COOEt$	181-183	63
40		powder	93

TABLE 4b

Reference Example No.	^{1}H-NMR (200MH$_2$, CDCl$_3$)δ
33	0.96(3H, t), 1.24(3H, t), 1.3-1.5(2H, m), 1.5-1.7(2H, m), 2.66(2H, q), 4.04(2H, t), 5.01(2H, s), 7.00(1H, s), 6.8-7.5(22H, m), 7.9-8.0(1H, m)
34	1.22(3H, t), 2.65(2H, q), 5.00(2H, s), 5.23(2H, s), 7.00(1H, s), 6.8-8.0(28H, m)
35	1.24(3H, t), 1.27(3H, t), 2.66(2H, q), 4.11(2H, q), 5.01(2H, s), 6.8-7.5(23H, m), 7.9-8.0(1H, m),
36	1.28(3H, t), 2.72(2H, q), 5.03(2H, s), 6.8-8.0(28H, m)
37	1.26(3H, t), 2.68(2H, q), 5.06(2H, q), 6.8-8.0(27H, m)
38	1.23(3H, t), 1.2-2.6(10H, m), 2.65(2H, q), 4.8-5.0(1H, m), 4.97(2H, s), 6.8-7.9(24H, m)
39	1.23(3H, t), 1.29(3H, t), 2.65(2H, q), 4.24(2H, q), 4.79(2H, s), 5.02(2H, s), 6.8-8.0(24H, m)
40	1.23(3H, t), 2.64(2H, q), 2.7-3.2(10H, m), 3.85(3H, s), 4.2-4.4(2H, m), 5.03(2H, s), 6.8-7.5(27H, m), 7.9-8.0(1H, m)

Working Example 1

A: Ethyl 2-ethyl-7-[2'-cyanobiphenyl-4-yl)methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

Ethyl 2-ethyl-4-hydroxythieno[2,3-b]-pyridine-5-carboxylate (250 mg, 1 mmol) and 4-(2'-cyanophenyl)benzyl chloride (250 mg, 1.1 mmol) were dissolved in 5 ml of N,N-dimethylformamide (DMF). To the solution was added potassium carbonate (150 mg) and the mixture was stirred at 90 °C for 2 hours. The reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/dichloromethane (1:1) to give 254 mg (60 %) of the title compound as crystals.

NMR ($CDCl_3$) δ : 1.30(3H, t, J=6Hz), 1.39(3H, t, J=6Hz), 2.81(2H, q, J=6, 15Hz), 4.40(2H, q, J=6, 13.5Hz), 5.27(2H, s), 7.25-8.0(9H, m), 8.37(1H, s).

B: Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate and 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid

A solution of the compound (250 mg, 0.59 mmol) prepared in Working Example 1A, sodium azide (390 mg, 5.9 mmol) and ammonium chloride (300 mg, 5.9 mmol) in DMF (15 ml) was stirred at 110 °C for 10 days. After cooling, the reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (9:1) to give 37 mg (13 %) of ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate as pale yellow powders.
IR (KBr)cm^{-1}: 1720, 1600, 1550, 1505.

NMR (CD_3OD) δ : 1.31(3H, t, J=7.6Hz), 1.36(3H, t, J=7.0Hz), 2.85(2H, q, J=7.6, 15.0Hz), 4.33(2H, q, J=7.0, 14.2Hz), 5.45(2H, s), 7.15(2H, d, J=8.6Hz), 7.21(1H, s), 7.28(2H, d, J=8.6Hz), 7.5-7.7(4H, m), 8.75(1H, s).

The column was further eluted with chloroform/methanol (9:1) to give 7 mg (2.7 %) of 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid as white solids.
IR (KBr)cm^{-1}: 1650, 1605, 1580, 1540, 1505.

NMR (CD_3OD) δ : 1.34(3H, t, J=7.6Hz), 2.89(2H, q, J=8.6, 15.0Hz), 5.47(2H, s), 7.15(2H, d, J=8.2Hz), 7.24(1H, s), 7.28(2H, d, J=8.2Hz), 7.5-7.7(4H, m).

Working Example 2

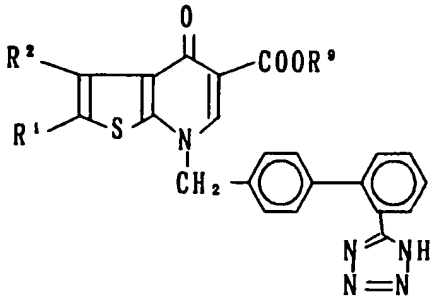
Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

A solution of the compound (727 mg, 1 mmol) prepared in Reference Example 4 in 20 ml of trifluoroacetic acid/water (1:3) was stirred at room temperature for 1 hour. The reaction mixture was poured into water followed by extraction with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (9:1) to give 1.28 g (86 %) of the title compound as colorless crystals. This product was identified by comparing with NMR and IR spectra of the compound obtained in Working Example 1B.
M.p. 161-164 °C.

Elemental Analysis for $C_{26}H_{23}N_5O_3S \cdot H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 62.01;	H, 5.00;	N, 13.91
Found:	C, 62.05;	H, 4.59;	N, 13.78

The following compounds as listed in Table 5 were prepared in the same manner as in Working Examples 2.

TABLE 5a



Working Example No.	R^1	R^2	R^9	mp (°C)	IR(KBr) (cm^{-1})
3	Br	H	Et	254-260 (decomp.)	1725, 1680, 1610, 1560, 1500
4	H	H	Et	245-249	1720, 1600, 1560
5	Me	H	Et	249-253	1710, 1675, 1605, 1560, 1505
6	n-Pr	H	Et	108-110	1720, 1605, 1550, 1505
7	Et	H	i-Bu	256-259 (decomp.)	1720, 1670, 1605, 1560, 1500
8	Et	H	CH_2CH_2OMe	201-210	1720, 1680, 1605, 1560, 1505
9	Et	NO_2	Et	214 ~ (decomp.)	1720, 1700, 1615, 1550, 1510

TABLE 5b

Working Example No.	NMR (DMSO-d_6) δ	E. Anal. (Calcd/Found) C(%), H(%),N(%)
3	1.29(3H,t,J=7.2Hz),4.24(2H,q, J=7.2,14.2Hz),5.46(2H,s),7.13(2H, d,J=8.2Hz),7.29(2H,d,J=8.2Hz), 7.5-7.7(5H,m),8.79(1H,s)	$C_{24}H_{18}BrN_5O_3S$ 53.74;3.38;13.06 53.57;3.34;12.80
4	1.29(3H,t,J=7.2Hz),4.24(2H,q, J=7.2,14.2Hz),5.51(2H,s),7.13(2H, d,J=8.0Hz),7.27(2H,d,J=8.0Hz), 7.3-7.8(8H,m),8.80(1H,s)	$C_{24}H_{19}N_5O_3S \cdot 0.5H_2O$ 61.79;4.32;15.01 61.94;4.17;14.80
5	1.29(3H,t,J=7.2Hz),2.44(3H,d, J=1.0Hz),4.23(2H,q,J=7.2,14.2Hz), 5.45(2H,s),7.08(1H,d,J=1.0Hz), 7.13(2H,d,J=8.0Hz),7.25(2H,d, J=8.0Hz),7.5-7.7(4H,m),8.74(1H,s)	$C_{25}H_{21}N_5O_3S$ 63.68;4.49;14.85 63.39;4.47;14.67
6	0.91(3H,t,J=7.2Hz),1.28(3H,t, J=7.0Hz),1.61(2H,q,J=7.2,15.0Hz), 2.76(2H,t,J=7.6Hz),4.23(2H,q, J=7.0,14.2Hz),5.45(2H,s),7.10(1H, s),7.12(2H,d,J=8.4Hz),7.26(2H,d, J=8.4Hz),7.5-7.7(4H,m), 8.74(1H,s)	$C_{27}H_{25}N_5O_3S \cdot H_2O$ 62.65;5.26;13.53 62.55;4.84;13.38
7	0.96(6H,d,J=6.8Hz),1.23(3H,t, J=7.4Hz),1.9-2.1(1H,m),2.80(2H, q,J=7.4,15.0Hz),3.97(2H,d, J=6.6Hz),5.46(2H,s),7.11(1H, s),7.13(2H,d,J=8.0Hz),7.27(2H,d, J=8.0Hz),7.5-7.7(4H,m), 8.70(1H,s)	$C_{28}H_{27}N_5O_3S \cdot 0.5H_2O$ 64.35;5.40;13.40 64.22;5.24;13.47
8	1.23(3H,t,J=7.4Hz),2.81(2H,q, J=7.4,15.0Hz),3.30(3H,s),3.62 2H,t,J=4.8Hz),4.31(2H,t,J=4.8Hz) 5.46(2H,s),7.11(1H,s),7.12(2H,d, J=8.0Hz),7.25(2H,d,J=8.0Hz), 7.5-7.7(4H,m),8.73(1H,s)	
9	1.20(3H,t,J=7.4Hz),1.29(3H,t, J=7.0Hz),2.83(2H,q,J=7.4,15.4Hz), 4.24(2H,q,J=7.0,14.0Hz),5.53(2H, s),7.14(2H,d,J=8.2Hz),7.30(2H,d, J=8.2Hz),7.5-7.7(4H,m),8.86(1H,s)	$C_{26}H_{22}N_6O_5S \cdot H_2O$ 56.93;4.41;15.32 57.12;4.05;15.26

Working Example 10

2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid

Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (600 mg, 1.235 mmol) was dissolved in 6 ml of 1N sodium hydroxide and the mixture was heated at 100 °C for 20 minutes with stirring. After cooling, 7 ml of 1N hydrochloric acid was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting crystal was washed with dichloromethane and dried 550 mg of the title compound as colorless crystals. This product was identified by comparing with NMR and IR spectra of the compound obtained in Working Example 1B. M.p. 153-157 °C.

Elemental Analysis for $C_{24}H_{19}N_5O_3S \cdot 3.5H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 55.38;	H, 5.03;	N, 13.48
Found:	C, 54.75;	H, 3.93;	N, 13.15

Working Example 11

A: Ethyl 2-ethyl-7-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

A mixture of ethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (200 mg, 0.8 mmol), 4-(2-t-butoxycarbonylphenyl)benzyl bromide (300 mg, 0.9 mmol) and cesium carbonate (650 mg, 2.0 mmol) in DMF (10 ml) was stirred at 60 °C for 3 hours and further at 100 °C for an additional hour. After cooling, the reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel to give 258 mg (62 %) of the title compound as crystals.
IR (KBr)cm^{-1}: 1720, 1705, 1690, 1510.

NMR ($CDCl_3$) δ : 1.20(9H, s), 1.32(3H, t, J=7.6Hz), 1.41(3H, t, J=7.2Hz), 2.81(2H, q, J=7.6, 14.6Hz), 4.40(2H, q, J=7.2, 14.2Hz), 5.23(2H, s), 7.2-7.5(8H, m), 7.81(1H, dd, J=1.6, 7.6Hz), 8.42(1H, s).

Elemental Analysis for $C_{30}H_{31}NO_5S$			
	C (%)	H (%)	N (%)
Calcd:	C, 69.61;	H, 6.04;	N, 2.71
Found:	C, 69.85;	H, 6.15;	N, 2.37

B: Ethyl 2-ethyl-7-[(2'-carboxybiphenyl-4-yl)methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

To 5 ml of trifluoroacetic acid under ice-cooling were added the compound (200 mg, 0.39 mmol) prepared in Working Example 11A and anisole (0.1 ml) and the mixture was stirred for 2.5 hours. The reaction mixture was concentrated to dryness in vacuo. To the resulting residue was added dichloromethane followed by evaporation to dryness in vacuo. These treatments were repeated twice and ether was added to the resulting residue to precipitate solids which were filtered and dried to give 167 mg (93 %) of the title compound as pale yellow powders.
IR (KBr)cm^{-1}: 1715, 1680, 1605.

NMR (d_6-DMSO) δ : 1.23(3H, t, J=7.4Hz), 1.29(3H, t, J=7.2Hz), 2.80(2H, q, J=7.4, 15.0Hz), 4.23(2H, q, J=7.2, 13.8Hz), 5.49(2H, s), 7.11(1H, s), 7.3-7.6(7H, m), 7.73(1H, d, J=7.4Hz), 8.77(1H, s).

Elemental Analysis for $C_{28}H_{23}NO_5S \cdot 0.3H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 66.88;	H, 5.09;	N, 3.00
Found:	C, 67.03;	H, 5.14;	N, 2.95

Working Example 12

2-Ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-B]pyridin-4(7H)-one

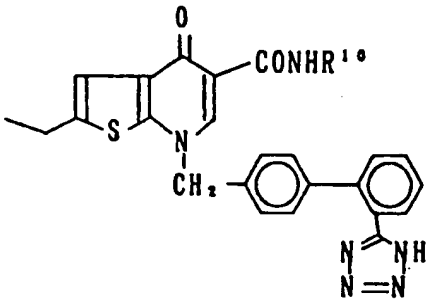
A mixture of the compound (123 mg, 0.25 mmol) prepared in Working Example 2 and benzylamine (2 ml) was stirred at 60 °C for 3 days. After cooling, the reaction mixture was poured into chloroform, washed twice with 1N hydrochloric acid, dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (19:1 to 9:1) to give 63 mg (45 %) of the title compound as crystals.
m p 177-180 °C.
IR (KBr)cm^{-1}: 1650, 1590, 1550, 1500.

NMR (DMSO-d_6)δ : 1.25(3H, t, J=7.4Hz), 2.83(2H, q, J=7.4Hz, 14.2Hz), 4.56(2H, d, J=5.8Hz), 5.57(2H, s), 7.0-7.7(14H, m), 8.95(1H, s).

Elemental Analysis for $C_{31}H_{26}N_6O_2S$			
	C (%)	H (%)	N (%)
Calcd:	C, 68.11;	H, 4.79;	N, 15.37
Found:	C, 68.06;	H, 4.79;	N, 15.17

The following compounds as listed in Table 6 were prepared in the same manner as in Working Examples 12.

TABLE 6a



Working Example No.	R^{10}	mp (°C)	IR(KBr) (cm^{-1})
13	H	267-270	1635, 1575, 1540, 1500
14	$CH_2CH(Me)_2$	248-251 (decomp.)	1655, 1590, 1555, 1525, 1510
15	CH_2CH_2OH	155-159	1655, 1595, 1550, 1520
16	C_6H_5	215-218	1655, 1595, 1545, 1505

TABLE 6b

Working Example No.	NMR (DMSO-d_6) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
13	1.25(3H,t,J=7.6Hz),2.83(2H,q, J=7.6,14.8Hz),5.54(2H,s),7.12(2H, d,J=8.2Hz),7.22(1H,s),7.26(2H,d, J=8.2Hz),7.5-7.7(4H,m),8.91(1H,s), 9.46(1H,bs)	$C_{24}H_{20}N_6O_2S \cdot H_2O$ 60.75;4.67;17.71 61.09;4.41;17.37
14	0.93(6H,d,J=6.6Hz),1.25(3H,t, J=7.4Hz),1.7-1.9(1H,m),2.84(2H,d, J=7.4,14.0Hz),3.18(2H,t,J=6.2Hz), 5.55(2H,s),7.11(2H,d,J=8.2Hz), 7.19(1H,s),7.25(2H,d,J=8.2Hz), 7.5-7.7(4H,m),8.90(1H,s)	$C_{28}H_{28}N_6O_2S \cdot H_2O$ 63.38;5.70;15.84 63.70;5.44;15.50
15	1.25(3H,t,J=7.4Hz),2.84(2H,q, J=7.4,16.0Hz),3.3-3.6(4H,m), 4.81(1H,bs),5.55(2H,s),7.11(2H, d,J=8.2Hz),7.18(1H,s),7.24(2H,d J=8.2Hz),7.5-7.7(4H,m),8.31(1H,s), 8.90(1H,s)	
16	1.27(3H,t,J=7.4Hz),2.87(2H,q, J=7.4,14.6Hz),5.59(2H,s),7.0-7.8 (14H,m),9.05(1H,s)	$C_{30}H_{24}N_6O_2S \cdot 0.5H_2O$ 66.53;4.65;15.52 66.28;4.51;15.26

Working Example 17

Ethyl 3-acetylamino-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate

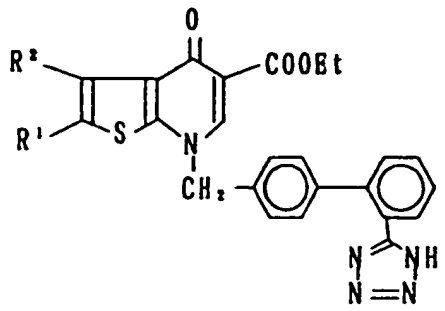
Ethyl 2-ethyl-3-nitro-7-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (200 mg, 0.26 mmol) was dissolved in a mixture of acetic anhydride (6 ml), acetic acid (6 ml), dioxane (4 ml) and tetrahydrofuran (5 ml) and the solution was heated to 70 °C. To the heated solution were added zinc powders (85 mg) and the reaction mixture was stirred for 2 hours. The insoluble material was removed from the reaction mixture by filtration and the filtrate was concentrated to dryness in vacuo. The resulting oil was dissolved in a mixture of trifluoroacetic acid (8 ml) and water (1 ml) and the solution was stirred at room temperature for 5 hours. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (20:1) to give 59 mg (42 %) of the title compound as white crystals.
m p 163-166 °C.
IR (KBr)cm^{-1} : 1720, 1700, 1615, 1550, 1510.

NMR ($CDCl_3$) δ : 1.14(3H, t, J=7.4Hz), 1.29(3H, t, J=7.0Hz), 2.03(3H, s), 2.63(2H, q, J=7.4, 15.0Hz), 4.23(2H, q, J=7.0, 14.2Hz), 5.45(2H, s), 7.13(2H, d, J=8.2Hz), 7.28(2H, d, J=8.2Hz), 7.5-7.7(4H, m), 8.74(1H, s), 9.66(1H, Bs).

Elemental Analysis for $C_{28}H_{26}N_6O_4S \cdot H_2O$			
	C (%)	H (%)	N (%)
Calcd:	C, 59.99;	H, 5.03;	N, 14.99
Found:	C, 59.50;	H, 4.56;	N, 14.76

The following compounds (Working Examples 18- 20) as listed in Table 7 were prepared in the same manner as in Working Examples 12.

TABLE 7a



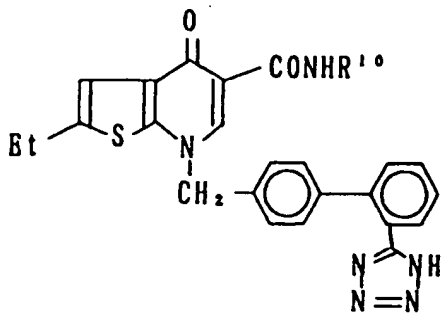
Working Example No.	R¹	R²	mp (°C)	Yield (%)
18	H	Me	167-170	30
19	Br	Me	227-231	77
20	CN	H	250-256	20

TABLE 7b

Working Example No.	NMR (DMSO-d_6) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
18	1.28(3H,t),2.47(3H,s),4.22(2H,q), 5.44(2H,s),6.92(1H,s),7.10(2H,d), 7.23(2H,d),7.5-7.7(4H,m),8.70(1H, s)	$C_{25}H_{21}N_5O_3S \cdot 0.2H_2O$ 63.20;4.54;14.74 63.00;4.37;14.80
19	1.29(3H,t),2.45(3H,s),4.23(2H,q), 5.43(2H,s),7.13(1H,d),7.27(2H,d), 7.5-7.8(4H,m),8.73(1H,s)	$C_{25}H_{20}BrN_5O_3S$ 54.55;3.66;12.72 54.82;3.63;12.83
20	1.29(3H,t),4.25(2H,q),5.52(2H,s), 7.13(2H,d),7.31(2H,d),7.5-7.8 (4H,m),8.25(1H,s),8.89(1H,s)	

The following compounds (Working Examples 21-36) were prepared in the same manner as in Working Example 12.

TABLE 8a



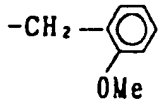
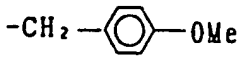
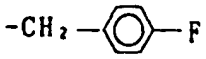
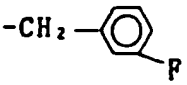
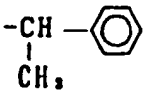
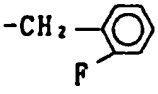
Working Example No.	R^{10}	mp (°C)	Yield (%)
21		134-148	42
22		223-225	67
23		202-204	54
24		powder	72
25		154-157	55
26		146-149	33

TABLE 8a

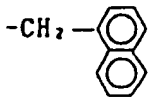
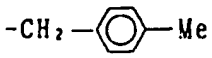
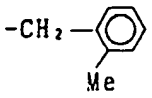
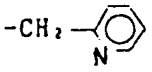
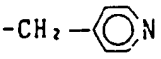
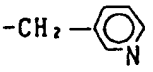
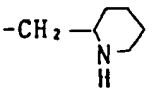
Working Example No.	R^{10}	mp (°C)	Yield (%)
27		170-173	45
28		207-209	62
29		150-154	57
30		223-226	38
31		205-209	30
32		244-248	63
33		powder	72

TABLE 8b

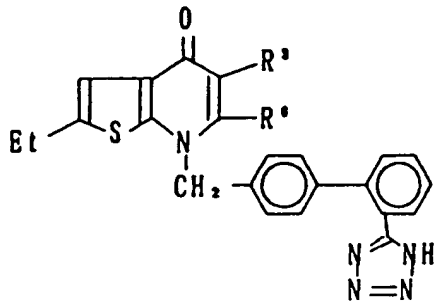
Working Example No.	NMR (200MHz, $CDCl_3$) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
21	1.36(3H,t),2.89(2H,q),3.88(3H,s), 4.61(2H,d),5.12(2H,s),6.8-7.6 (12H,m),8.05-8.15(1H,m),8.30(1H,s)	
22	1.37(3H,t),2.89(2H,q),3.78(3H,s), 4.57(2H,s),5.20(2H,s),7.6-8.0 (13H,m),8.39(1H,s)	$C_{32}H_{28}N_6O_3S \cdot H_2O$ 64.63;5.08;14.13 64.92;4.74;13.99
23	1.38(3H,t),2.91(2H,q),4.60(2H,d), 5.18(2H,s),6.9-7.6(12H,m),8.1-8.2 (1H,m),8.29(1H,s),10.99(1H,brs)	$C_{31}H_{25}FN_6O_2S$ 65.94;4.46;14.88 65.94;4.45;14.71
24	1.37(3H,t),2.90(2H,q),4.61(2H,d), 5.16(2H,s),6.8-7.6(12H,m), 8.05-8.15(1H,m),8.34(1H,s)	
25	1.38(3H,t),1.58(3H,d),2.91(2H,q), 5.13(2H,s),5.22(1H,t),7.1-7.6 (13H,m),8.1-8.2(1H,m),8.20(1H,s), 11.05(1H,bs)	$C_{32}H_{28}N_6O_2S \cdot 0.5H_2O$ 67.47;5.13;14.75 67.64;4.99;14.52
26	1.37(3H,t),2.90(2H,q),4.67(2H,d), 5.16(2H,s),7.0-7.6(12H,m),8.05-8.15(1H,m),8.29(1H,s),10.97 (1H,brs)	$C_{31}H_{25}FN_6O_2S \cdot 1.5H_2O$ 62.93;4.77;14.20 63.02;4.30;14.03

TABLE 8b

Working Example No.	NMR (200MHz) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
27	1.35(3H,t),2.86(2H,q),5.07(2H,s), 5.10(2H,s),7.1-7.9(14H,m),8.07 (2H,d),8.31(1H,brs),11.01(1H,brs) ;(CDCl$_3$)	$C_{35}H_{28}N_6O_2S \cdot 0.5H_2O$ 69.40;4.83;13.87 69.40;4.65;13.64
28	1.37(3H,t),2.31(3H,s),2.90(2H,q), 4.57(2H,d),5.15(2H,s),7.0-7.6 (12H,m),8.0-8.2(1H,m),8.27(1H,brs) ;(CDCl$_3$)	$C_{32}H_{28}N_6O_2S \cdot 0.5H_2O$ 67.47;5.13;14.75 67.54;5.14;14.57
29	1.37(3H,t),2.38(3H,s),2.90(2H,q), 4.61(2H,d),5.16(2H,s),7.0-7.6 (12H,m),8.0-8.2(1H,m),8.25(1H,brs) ;(CDCl$_3$)	$C_{32}H_{28}N_6O_2S \cdot 0.2H_2O$ 68.11;5.07;14.89 68.01;4.85;14.94
30	1.32(3H,t),2.83(3H,q),4.65(2H,d), 5.35(2H,s),7.0-8.1(13H,m),9.34(1H, s),11.05(1H,t);(CDCl$_3$)	$C_{30}H_{25}N_7O_2S \cdot HCl$ $0.5H_2O$ 60.75;4.59;16.53 60.83;4.29;16.36
31	1.38(3H,t),2.91(2H,q),4.90(2H,s), 5.34(2H,s),7.20(2H,d),7.28(2H,d), 7.37(1H,s),7.5-7.8(4H,m),7.96(2H, d),8.62(1H,s),8.78(2H,d);(CDCl$_3$)	SIMS; 548(MH$^+$)
32	1.25(3H,t),2.85(2H,q),4.73(2H,d), 5.57(2H,s),7.12(2H,d),7.20(1H,s), 7.26(2H,d),7.5-8.9(8H,m),8.93(1H, s),10.71(1H,t);(DMSO-d_6)	$C_{30}H_{25}N_7O_2S \cdot HCl$ $\cdot 0.5H_2O$ 58.11;4.88;15.81 57.86;4.34;15.60
33	1.26(3H,t),1.3-1.9(6H,m),2.86(2H, q),3.0-3.7(5H,m),5.57(2H,s),7.14 (2H,d),7.21(1H,s),7.23(2H,d), 7.4-7.7(4H,m),8.6(1H,brs),8.91(1H, s),10.40(1H,t);(DMSO-d_6)	SIMS; 554(MH$^+$)

The following compounds (Working Examples 34-41) were prepared in the same manner as in Working Example 12.

TABLE 9a



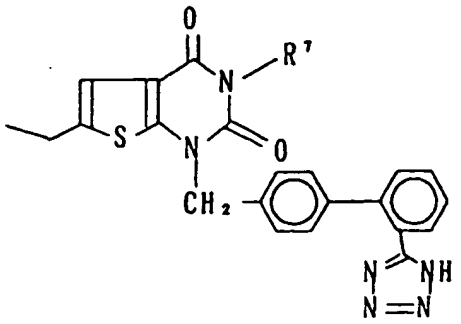
Working Example No.	R^3	R^6	mp (°C)	Yield (%)
34	$-CH_2OH$	H	>260 (dec.)	73
35	H	H	249-253	83
36	-CHO	H	powder	66
37	-CH=CHCOOtBu	H	powder	100
38	$-CH_2OMe$	H	213-216	82
39	-COOH	CH_3	162-167	
40	-CONH- 	CH_3	175-180	
41	-COOMe	$-CH_2COOMe$		

TABLE 9b

Working Example No.	NMR (200MHz) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
34	1.24(3H,t),2.79(2H,q),4.40(2H,s), 7.05(1H,s),7.11(2H,d),7.22(2H,d), 7.5-7.8(4H,m),7.98(1H,s);(DMSO-d_6)	$C_{24}H_{21}N_5O_2S \cdot 0.8H_2O$ 62.95;4.97;15.29 63.18;4.88;14.86
35	1.24(3H,t),2.80(2H,q),5.35(2H,s), 6.21(1H,d),7.07(1H,s),7.11(2H,d), 7.24(2H,d),7.4-7.8(4H,m), 8.08(1H,d);(DMSO-d_6)	$C_{23}H_{19}N_5OS \cdot H_2O$ 64.02;4.91;16.23 63.87;4.44;15.90
36	1.24(3H,t),2.82(2H,q),5.50(2H,s), 7.12(2H,d),7.20(1H,s),7.28(2H,d), 7.5-7.7(4H,m),8.69(1H,s),10.28(1H, s);(DMSO-d_6)	
37	1.25(3H,t),1.37(9H,s),2.80(2H,q), 5.35(2H,s),6.93(1H,d),7.1-7.9(10H, m),8.55(1H,s);(DMSO-d_6)	
38	1.21(3H,t),2.69(2H,q),3.44(3H,s), 4.09(2H,s),5.21(2H,s), 6.8-7.9(10H,m);($CDCl_3$)	$C_{25}H_{23}N_5O_2S \cdot 0.7H_2O$ 63.87;5.23;14.90 64.00;4.99;14.69
39	1.27(3H,t),2.88(2H,q),2.95(3H,s), 5.68(2H,s),7.11(4H,s),7.29(1H,s), 7.5-7.8(4H,m);(DMSO-d_6)	$C_{25}H_{21}N_5O_3S \cdot 0.5H_2O$ 62.49;4.61;14.57 62.28;4.36;14.39
40	1.39(3H,t),2.75(3H,s),2.99(2H,q), 5.85(2H,s),7.1-7.8(14H,m);(CD_3OD)	SIMS; 547(MH^+)
41	1.32(3H,t),2.86(2H,q),3.66(3H,s), 3.88(3H,s),3.94(2H,s),5.55(2H,s), 6.98(2H,d),7.13(2H,d),7.22(1H,s) 7.4-7.7(4H,m);(CD_3OD)	SIMS; 544(MH^+)

The following compounds (Working Examples 42-48) were prepared in the same manner as in Working Example 2.

TABLE 10a



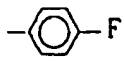
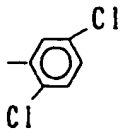
Working Example No.	R^7	mp (°C)	Yield (%)
42	Bu	127-130	32
43	$-CH_2-$ 	202-205	65
44	Et	210-212	59
45		246-250	70
46		powder	31
47		207-221	57
48	$-CH_2COOEt$	167-169	44

TABLE 10b

Working Example No.	^{1}H-NMR ($CDCl_3$) δ	E. Anal. (Calcd/Found) C(%), H(%), N(%)
42	0.92(3H,t),1.30(3H,t),1.2-1.5(2H, m),1.5-1.8(2H,m),2.77(2H,q),4.01 (2H,t),5.15(2H,s),7.00(1H,s), 7.23(2H,d),7.42(2H,d),7.5-7.7(3H, m),8.1-8.2(1H,m)	$C_{26}H_{26}N_6O_2S$ 64.18;5.39;17.27 64.00;5.51;17.18
43	1.21(3H,t),2.75(2H,q),5.12(2H,s), 5.15(2H,s),7.02(1H,s),7.09(2H,d), 7.2-7.8(11H,m)	$C_{29}H_{24}N_6O_2S \cdot 0.4H_2O$ 65.99;4.74;15.92 66.17;4.91;15.63
44	1.25(3H,t),1.30(3H,t),2.78(2H,q), 4.08(2H,q),5.16(2H,s),7.01(1H,s), 7.23(2H,d),7.43(2H,d),7.5-7.7(3H, m),8.1-8.2(1H,m)	$C_{24}H_{22}N_6O_2S \cdot 0.5H_2O$ 61.65;4.96;17.97 61.70;4.83;17.80
45	1.32(3H,t),2.81(2H,q),5.14(2H,s), 7.06(1H,s),7.1-7.8(12H,m)	$C_{28}H_{21}FN_6O_2S$ 64.11;4.04;16.02 63.82;3.97;15.77
46	1.33(3H,t),2.81(2H,q),5.20(2H,q), 7.07(1H,s),7.2-8.2(11H,m)	$C_{28}H_{20}N_6O_2SCl_2 \cdot 0.6H_2O$ 57.36;3.64;14.33 57.74;3.75;13.75
47	1.29(3H,t),1.2-2.6(10H,m),2.76 (2H,q),4.7-5.0(1H,m),5.13(2H,s), 6.99(1H,s),7.24(2H,d),7.42(2H,d), 7.5-7.7(3H,m),8.1-8.2(1H,m)	$C_{28}H_{28}N_6O_2S \cdot 0.4H_2O$ 64.69;5.58;16.17 64.81;5.50;15.95
48	1.29(3H,t),1.31(3H,t),2.79(2H,q), 4.23(2H,q),4.80(2H,s),5.17(2H,s), 7.03(1H,s),7.22(2H,d),7.4-7.7(5H, m),8.1-8.2(1H,m)	$C_{26}H_{24}N_6O_4S$ 60.45;4.68;16.27 60.33;4.59;16.17

Pharmaceutical Examples

The compounds (I) of the present invention are employed, for example, when used as agents for treating circulatory system diseases such as hypertension, heart diseases, strokes and the like, in the following formulations.

1. Capsule

(1) Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno-[2,3-b]pyridine-5-carboxylate	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
One capsule	180 mg

The ingredients (1), (2), and (3) and a half of the ingredient (4) were blended together and granulated. To this mixture was added the remaining half of the ingredient (4) and distributed into gelatine capsules.

2. Tablet

(1) Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno-[2,3-b]pyridine-5-carboxylate	10 mg
(2) Lactose	35 mg
(3) Maize starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
One tablet	230 mg

Two third each of the ingredients (1), (2), (3) and (4) and a half of the ingredient (5) were blended together and granulated. To these granules were added the remaining ingredients (4) and (5) and then compressed to form tablets.

3. Injection

(1) 2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid · sodium salt	10 mg
(2) Inositol	100 mg
(3) Benzyl alcohol	20 mg
One ampule	130 mg

The ingredients (1), (2) and (3) were dissolved in distilled water for injection to a total volume of two ml and distributed into ampules. Total processes were carried out under sterile conditions.

Experimental Example 1

Inhibition of binding of angiotensin-II to angiotensin receptor

[Method]

An experiment of inhibition on the binding of angiotensin-II (A-II) to A-II-receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685-696 (1978)]. An A-II-receptor was prepared from the membrane fraction of bovine adrenal cortex.

The compound of the present invention (10^{-9}M to 3×10^{-5}M) and ^{125}I-A-II (1.85 kBq/50 μ l) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-A-II were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-A-II bound to the receptor was measured.

[Results]

The results relating to the compounds of the present invention are shown in Table 11.

Experimental Example 2

Inhibitory effect of the compound of the present invention on pressor action of A-II

[Method]

Jcl : SD rats (9 week old, male) were used. On the day previous to the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed to access freely to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means

of polygraph. Before administration of the drug, the pressor action due to intravenous administration of A-II (100 ng/kg) as the control was measured. The drugs were orally administered, and then, at each point of the measurement, A-II was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on A-II-induced pressor action was evaluated.

[Results]

The results relating to the compounds of the present invention are shown in Table 11.

TABLE 11

Working Example No.	Radio Receptor Assay $IC_{50}(\mu M)$	Pressor Response (30 mg/Kg, p.o.)
2	0.05	NT*a
3	0.07	NT
4	0.20	NT
5	0.05	NT
6	0.09	NT
7	0.17	NT
8	0.01	NT
10	0.04	+*b
11	0.21	NT
12	0.06	++
13	0.02	NT
14	0.13	NT
15	0.05	NT
16	0.12	++
20	0.67	NT
21	0.25	++
23	0.17	++
24	0.19	++
25	0.78	++
26	0.21	++
28	0.22	+
29	0.12	++
30	0.02	++

*a : NT , not tested.

*b : (% Inhibition), ++ ≧ 70 % > + ≧ 50 %.

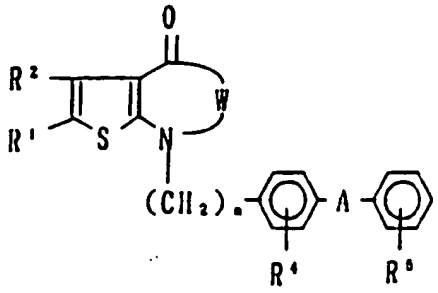
It is understood that the preceding representative examples may be varied within the scope of the present invention by one skilled in the art to achieve essentially the same results.

As many widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

Claims

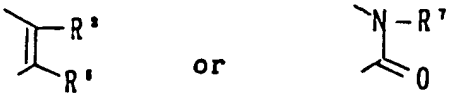
Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula:



(I)

wherein W is



R^1 and R^2 which may be the same or different, are each independently

(1) hydrogen,
(2) halogen,
(3) cyano,
(4) nitro,
(5) a group having the formula: R^8CONH- wherein R^8 is hydrogen or (C_{1-8})alkyl group which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or naphthyl, or
(6) a hydrocarbon residue selected from the group consisting of (i) (C_{1-8})alkyl, (ii) (C_{2-8})alkenyl, (iii) (C_{2-8})alkynyl, (iv) (C_{3-8})cycloalkyl, (v) an aromatic hydrocarbon selected from the group consisting of phenyl and naphthyl, wherein said hydrocarbon residue may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;

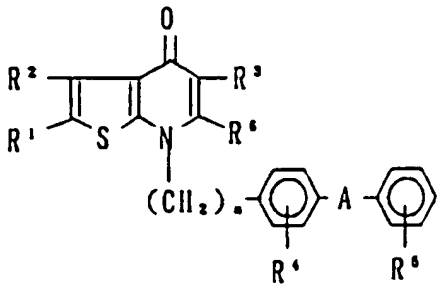
R^3 is

(1) hydrogen,
(2) (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino, or

(3) -COD wherein D is hydrogen, C_{1-4}-alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino, wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro or lower (C_{1-4}) alkoxy;

R^4 is hydrogen, halogen or nitro;
R^5 is carboxyl, lower (C_{1-4})alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;
R^6 is hydrogen or (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;
R^7 is a hydrocarbon residue which may be substituted like R^1 and R^2; A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group selected from the group consisting of (C_{1-4})alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2-, or -CH=CH-; and n is an integer of 1 or 2; and a pharmaceutically acceptable salt thereof.

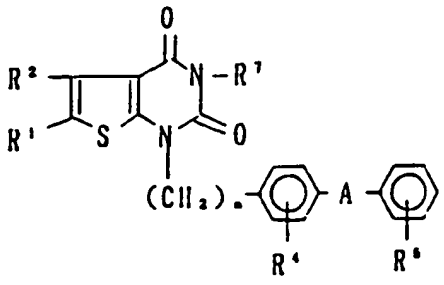
2. A compound according to claim 1, which is a compound of the formula (Ia):



(Ia)

wherein R^1 and R^2 are as defined in claim 1;
R^3 is hydrogen, formyl, optionally substituted alkyl or alkenyl as defined in claim 1, or -COD wherein D is alkoxy, hydroxy, halogen, or optionally substituted amino as defined in claim 1;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined in claim 1;
R^6, A and n are as defined in claim 1
and a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, which is a compound of the formula (Ib):



(Ib)

wherein R^1 and R^2 are as defined in claim 1;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined in claim 1;
R^7, A and n are as defined in claim 1;
and a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein an optionally substituted amino as defined in claim 1 for the substituents of said hydrocarbon residue is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, or N-(m-methoxy)phenylpiperazino.

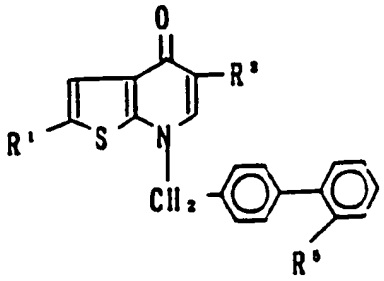
5. A compound according to claim 1, wherein said D' is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino.

6. A compound according to claim 1, wherein said D is amino, N- (C_{1-4}) alkyl amino, N,N-di (C_{1-4})alkyl amino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, or N-(p-fluorophenyl)piperazino wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro or lower (C_{1-4})alkoxy.

7. A compound according to claim 1 , wherein said R^5 is tetrazolyl.

8. A compound according to claim 1 , wherein said R^5 is in the ortho position.

9. A compound according to claim 1, which is a compound of the formula (Ia'):



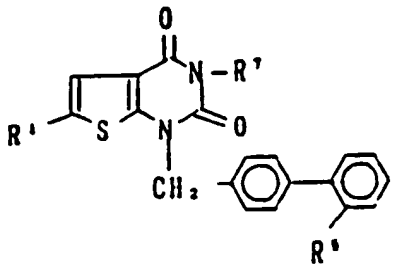
(Ia')

wherein R^1 is (C_{1-8})alkyl; R^3 is

(1) hydrogen,
(2) (C_{1-8})alkyl which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy or -COD" wherein D" is (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino, or
(3) -COD wherein D is hydrogen, (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino; and R^5 is carboxyl or tetrazolyl;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1, which is a compound of the formula (Ib'):



(Ib')

wherein R^1 is (C_{1-8})alkyl; R^7 is (C_{1-8})alkyl which may be optionally substituted with phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, or -COD' wherein D' is (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino or N-phenylpiperazino, (C_{3-8})cycloalkyl, or phenyl or naphthyl which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;
and R^5 is carboxyl or tetrazolyl;
or a pharmaceutically acceptable salt thereof.

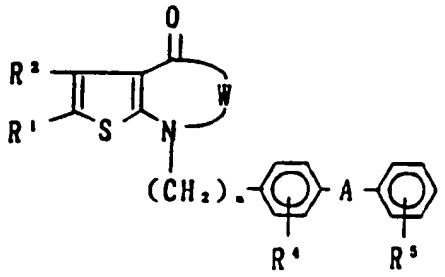
11. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate, 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid, methoxyethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate, 2-ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one, 2-ethyl-5-(N-phenylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one, and 2-ethyl-5-(N-2-pyridylmethylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one.

12. A compound according to claim 10, wherein R^1 is ethyl, R^5 is 1H-tetrazol-5-yl and R^7 is butyl, benzyl, ethyl, p-fluorophenyl, 2,5-dichlorophenyl, cyclohexyl, ethoxycarbonylmethyl, or 2-[4-(o-methoxyphenyl)-piperazino]ethyl.

13. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical acceptable carrier, excipient or diluent.

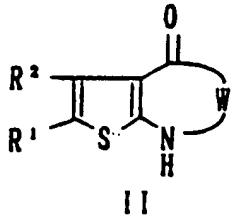
14. A use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

15. A method for producing a compound of the formula (I):



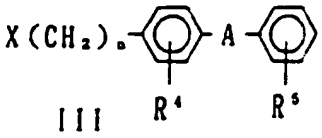
(I)

wherein W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, A and n Claim 1 have the meaning as defined in Claim 1 or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula (II):



II

wherein R^1, R^2, and W have the above-defined meanings, with a compound of the formula (III):

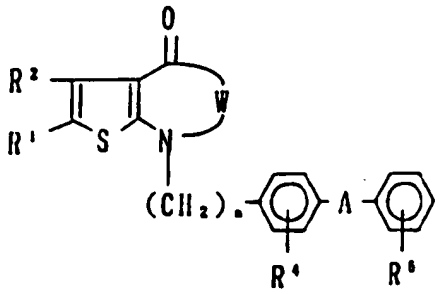


III

wherein R^4, R^5, A and n have the above-defined meanings, and X is halogen,
and, (i) if desired, converting a compound of the formula (I) wherein R^5 is cyano or protected tetrazolyl, and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, into a compound of the formula (I) wherein R^5 is tetrazolyl and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, (ii) if desired, converting a compound of the formula (I) wherein -R^3 is lower (C_{1-4}) alkoxycarbonyl or halogenocarbonyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is carboxyl, or optionally substituted carbamoyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, or (iii) if desired, converting a compound of the formula (I) wherein -R^3 is carboxyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is halogenocarbonyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

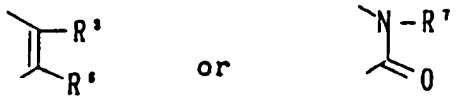
Claims for the following Contracting States : ES, GR

1. A method for producing a compound of the formula (I):



(I)

wherein W is



R^1 and R^2 which may be the same or different, are each independently

(1) hydrogen,
(2) halogen,
(3) cyano,
(4) nitro, (5) a group having the formula: R^8CONH- wherein R^8 is
hydrogen or (C_{1-8})alkyl group which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or naphthyl, or
(6) a hydrocarbon residue selected from the group consisting of (i) (C_{1-8})alkyl, (ii) (C_{2-8})alkenyl, (iii) (C_{2-8})alkynyl, (iv) (C_{3-8})cycloalkyl, (v) an aromatic hydrocarbon selected from the group consisting of phenyl and naphthyl, wherein said hydrocarbon residue may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;

R^3 is

(1) hydrogen,
(2) (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino, or
(3) -COD wherein D is hydrogen, C_{1-4}-alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino, wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro or lower (C_{1-4}) alkoxy;

R^4 is hydrogen, halogen or nitro;

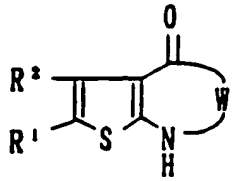
R^5 is carboxyl, lower (C_{1-4})alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid or sulfonic acid;

R^6 is hydrogen or (C_{1-8})alkyl or (C_{2-8})alkenyl, which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, halogen, lower (C_{1-4})alkoxy, or -COD" wherein D" is lower (C_{1-4})alkoxy, hydroxy, halogen, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkyl amino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino;

R^7 is a hydrocarbon residue which may be substituted like R^1 and R^2; A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group selected from the group consisting of (C_{1-4})alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2-, or -CH=CH-; and n is an integer of 1 or 2;

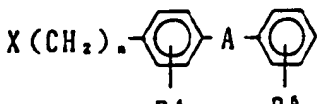
or a pharmaceutically acceptable salt thereof, which comprises

reacting a compound of the formula (II):



II

wherein R^1, R^2, and W have the above-defined meanings, with a compound of the formula (III):

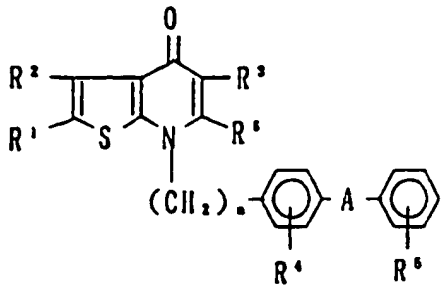


III

wherein R^4, R^5, A and n have the above-defined meanings, and X is halogen,

and, (i) if desired, converting a compound of the formula (I) wherein R^5 is cyano or protected tetrazolyl, and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, into a compound of the formula (I) wherein R^5 is tetrazolyl and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, (ii) if desired, converting a compound of the formula (I) wherein -R^3 is lower (C_{1-4}) alkoxycarbonyl or halogenocarbonyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is carboxyl, or optionally substituted carbamoyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, or (iii) if desired, converting a compound of the formula (I) wherein -R^3 is carboxyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is halogenocarbonyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

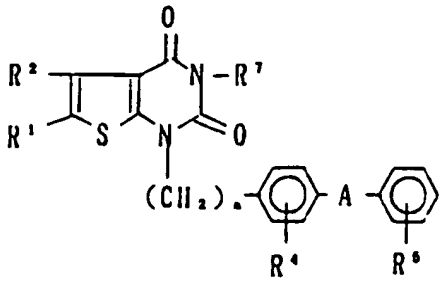
2. A method according to claim 1 for producing a compound of the formula (Ia):



(Ia)

wherein R^1 and R^2 are as defined in claim 1;
R^3 is hydrogen, formyl, optionally substituted alkyl or alkenyl as defined in claim 1, or -COD wherein D is alkoxy, hydroxy, halogen, or optionally substituted amino as defined in claim 1;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined in claim 1;
R^6, A and n are as defined in claim 1
and a pharmaceutically acceptable salt thereof.

3. A method according to claim 1 for producing a compound of the formula (Ib):



(Ib)

wherein R^1 and R^2 are as defined in claim 1;
R^4 is hydrogen, halogen or nitro;
R^5 is as defined in claim 1;
R^7, A and n are as defined in claim 1;
and a pharmaceutically acceptable salt thereof.

4. A method according to claim 1, wherein an optionally substituted amino as defined in claim 1 for the substituents of said hydrocarbon residue is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, or N-(m-methoxy)phenylpiperazino.

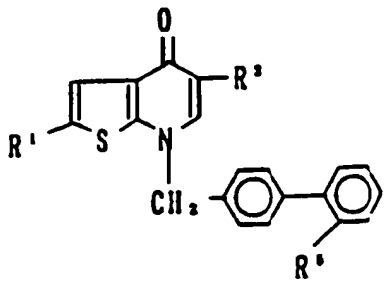
5. A method according to claim 1, wherein said D' is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino.

6. A method according to claim 1, wherein said D is amino, N- (C_{1-4}) alkyl amino, N,N-di (C_{1-4})alkyl amino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, or N-(p-fluorophenyl)piperazino wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, hydroxyl, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, halogen, nitro or lower (C_{1-4})alkoxy.

7. A method according to claim 1 , wherein said R^5 is tetrazolyl.

8. A method according to claim 1 , wherein said R^5 is in the ortho position.

9. A method according to claim 1 for producing a compound of the formula (Ia'):

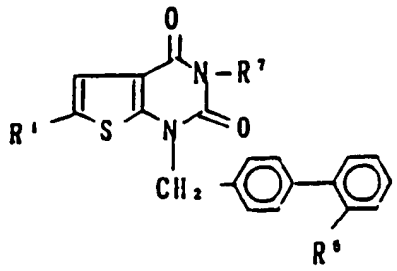


(Ia')

wherein R^1 is (C_{1-8})alkyl; R^3 is

(1) hydrogen,
(2) (C_{1-8})alkyl which may be straight or branched and may be optionally substituted with hydroxyl, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, halogen, (C_{1-4})alkoxy or -COD" wherein D" is (C_{1-4})alkoxy, hydroxy, halogen, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino, or
(3) -COD wherein D is hydrogen, (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkyl amino, N,N-dilower (C_{1-4})alkylamino, phenylamino, benzylamino, naphthylmethylamino, pyridylamino, pyridylmethylamino, morpholino, piperidino, piperazino, piperidylmethyl, N-(p-fluorophenyl)piperazino, or N-phenylpiperazino; and R^5 is carboxyl or tetrazolyl; or a pharmaceutically acceptable salt thereof.

10. A method according to claim 1 for producing a compound of the formula (Ib'):



(Ib')

wherein R^1 is (C_{1-8})alkyl; R^7 is (C_{1-8})alkyl which may be optionally substituted with phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, or -COD' wherein D' is (C_{1-4})alkoxy, hydroxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino or N-phenylpiperazino, (C_{3-8})cycloalkyl, or phenyl or naphthyl which may be substituted with hydroxyl, (C_{1-4})alkoxy, (C_{1-4})alkyl, halogen, nitro, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmethylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, N-(m-methoxy)phenylpiperazino, (C_{1-4})alkanoyloxy, benzoyloxy, phenyl which may be substituted with halogen, nitro, (C_{1-4})alkoxy, (C_{1-4})alkyl at an optional position on the phenyl ring, or a group having the formula: -COD' wherein D' is hydroxy, (C_{1-4})alkoxy, amino, N-lower (C_{1-4})alkylamino, N,N-dilower (C_{1-4})alkylamino, phenylamino, naphthylamino, benzylamino, naphthylmeth-

ylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino; and R^5 is carboxyl or tetrazolyl; or a pharmaceutically acceptable salt thereof.

11. A method according to claim 1 for producing a compound which is selected from the group consisting of ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate, 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid, methoxyethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate, 2-ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one, 2-ethyl-5-(N-phenylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one, and 2-ethyl-5-(N-2-pyridylmethylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-dihydrothieno[2,3-b]pyridin-4(7H)-one or a pharmaceutically acceptable salt thereof.

12. A method according to claim 10, wherein R^1 is ethyl, R^5 is 1H-tetrazol-5-yl and R^7 is butyl, benzyl, ethyl, p-fluorophenyl, 2,5-dichlorophenyl, cyclohexyl, ethoxycarbonylmethyl, or 2-[4-(o-methoxyphenyl)-piperazino]ethyl.

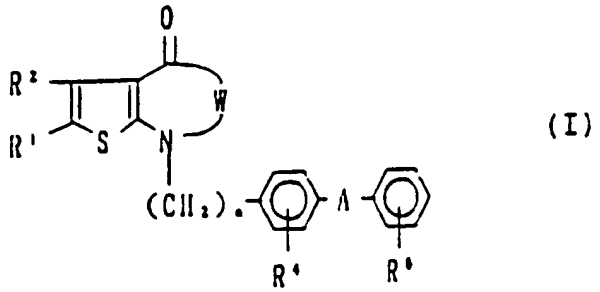
13. A method for producing a pharmaceutical composition for antagonizing angiotensin II which comprises admixing a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutical acceptable carrier, excipient or diluent.

14. A use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

Patentansprüche

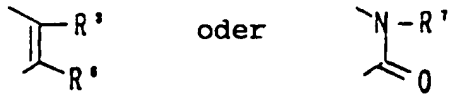
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



(I)

worin W



ist,
R^1 und R^2, die gleich oder verschieden sein können, jeweils unabhängig

(1) Wasserstoff,
(2) Halogen,
(3) Cyanoreste,
(4) Nitroreste,

(5) Gruppen mit der Formel R^8CONH-, worin R^8 Wasserstoff oder eine (C_1-C_8)-Alkylgruppe ist, die mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Benzylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position am Phenylring substituiert sein können, oder Naphthylresten substituiert sein kann, oder

(6) Kohlenwasserstoffreste sind, ausgewählt aus der Gruppe bestehend aus (i) (C_1-C_8)-Alkylresten, (ii) (C_2-C_8)-Alkenylresten, (iii) (C_2-C_8)-Alkinylresten, (iv) (C_3-C_8)-Cycloalkylresten, (v) einem aromatischen Kohlenwasserstoffrest ausgewählt aus der Gruppe bestehend aus Phenyl- und Naphthylresten, wobei der Kohlenwasserstoffrest mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position am Phenylring substituiert sein können, oder einer Gruppe der Formel -COD' substituiert sein kann, worin D' ein Hydroxy-, (C_1-C_4)-Alkoxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist;

R^3 (1) Wasserstoff,
(2) ein (C_1-C_8)-Alkyl- oder (C_2-C_8)-Alkenylrest, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Halogen-, Niedrig(C_1-C_4)alkoxyresten oder -COD" substituiert sein kann, worin D" ein Niedrig(C_1-C_4)-alkoxy-, Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist oder
(3) -COD ist, worin D Wasserstoff, ein (C_1-C_4)-Alkoxy-` Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-(p-Fluorphenyl)piperazino- oder N-Phenylpiperazinorest ist, worin die Alkyl-, Aryl- und Heteroarylgruppen gegebenenfalls mit Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sek.-Butyl-, Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)-alkylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, Halogen-, Nitro- oder Niedrig(C_1-C_4)alkoxyresten substituiert sein können;

R^4 Wasserstoff, Halogen oder ein Nitrorest ist;

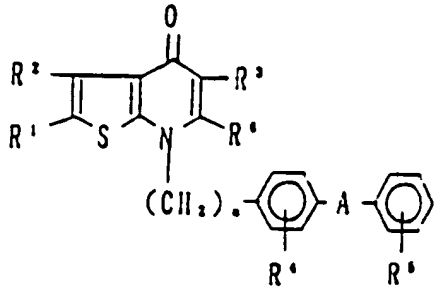
R^5 ein Carboxyl-, Niedrig(C_1-C_4)alkoxycarbonyl-, Cyano-, Tetrazolyl-, Trifluormethansulfonsäureamid-, Phosphorsäure- oder Sulfonsäurerest ist;

R^6 Wasserstoff oder ein (C_1-C_8)-Alkyl- oder (C_2-C_8)-Alkenylrest ist, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Halogen-, Niedrig(C_1-C_4)alkoxyresten oder -COD" substituiert sein kann, worin D" ein Niedrig(C_1-C_4)alkoxy-, Hydroxy-, Halogen-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist;

R^7 ein Kohlenwasserstoffrest ist, der wie R^1 und R^2 substituiert sein kann; A eine direkte Bindung oder ein Abstandshalter mit einer Atomlänge von 2 oder weniger zwischen der Phenylengruppe und der Phenylgruppe ist ausgewählt aus der Gruppe bestehend aus einem (C_1-C_4)-Alkylenrest, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2- oder -CH=CH- und n eine ganze Zahl von 1 oder 2 ist und

ein pharmazeutisch annehmbares salz davon.

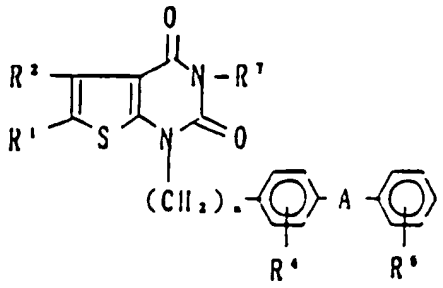
2. Verbindung nach Anspruch 1, die eine Verbindung der Formel (Ia) ist:



(Ia)

worin R^1 und R^2 wie in Anspruch 1 definiert sind;
R^3 Wasserstoff, ein Formylrest, ein gegebenenfalls substituierter Alkyl- oder Alkenylrest, wie in Anspruch 1 definiert, ist oder -COD ist, worin D ein Alkoxy-, Hydroxy-, Halogen- oder gegebenenfalls substituierter Aminorest, wie in Anspruch 1 definiert, ist;
R^4 Wasserstoff, Halogen oder ein Nitrorest ist;
R^5 wie in Anspruch 1 definiert ist;
R^6, A und n wie in Anspruch 1 definiert sind und ein pharmazeutisch annehmbares Salz davon.

3. Verbindung nach Anspruch 1, die eine Verbindung der Formel (Ib) ist:



(Ib)

worin R^1 und R^2 wie in Anspruch 1 definiert sind;
R^4 Wasserstoff, Halogen oder ein Nitrorest ist;
R^5 wie in Anspruch 1 definiert ist;
R^7, A und n wie in Anspruch 1 definiert sind und
ein pharmazeutisch annehmbares Salz davon.

4. Verbindung nach Anspruch 1, worin ein wie für die Substituenten des Kohlenwasserstoffrestes in Anspruch 1 definierter gegebenenfalls substuierter Aminorest ein Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Benzylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino- oder N-(m-Methoxy)-phenylpiperazinorest ist.

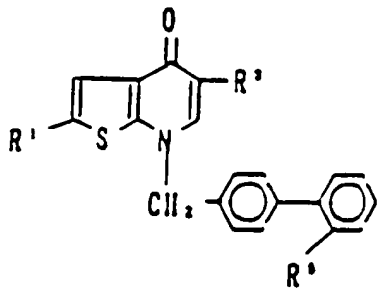
5. Verbindung nach Anspruch 1, worin D' ein Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Benzylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist.

6. Verbindung nach Anspruch 1, worin D ein Amino-, N-(C_1-C_4)Alkylamino-, N,N-Di(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-Phenylpiperazino- oder N-(p-Fluorphenyl)piperazinorest ist, worin die Alkyl-, Aryl- und Heteroarylgruppen gegebenenfalls mit Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sek.-Butyl-, Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, Halogen-, Nitro- oder Niedrig(C_1-C_4)alkoxyresten substituiert sein können.

7. Verbindung nach Anspruch 1, worin R^5 ein Tetrazolylrest ist.

8. Verbindung nach Anspruch 1, worin R^5 in ortho-Position ist.

9. Verbindung nach Anspruch 1, die eine Verbindung der Formel (Ia') ist:



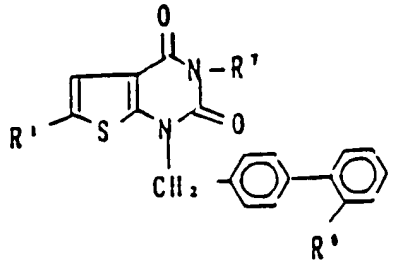
(Ia')

worin R^1 ein (C_1-C_8)-Alkylrest ist;
R^3

(1) Wasserstoff,
(2) ein (C_1-C_8)-Alkylrest ist, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig-(C_1-C_4)alkylamino-, Halogen-, (C_1-C_4)-Alkoxyresten oder -COD" substituiert sein kann, worin D" ein (C_1-C_4)-Alkoxy-, Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist oder
(3) -COD ist, worin D Wasserstoff, ein (C_1-C_4)-Alkoxy-, Hydroxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-(p-Fluorphenyl)piperazino- oder N-Phenylpiperazinorest ist und R^5 ein Carboxyl- oder Tetrazolylrest ist oder

ein pharmazeutisch annehmbares Salz davon.

10. Verbindung nach Anspruch 1, die eine Verbindung der Formel (Ib') ist:



(Ib')

worin R^1 ein (C_1-C_8)-Alkylrest ist; R^7 ein (C_1-C_8)-Alkylrest ist, der gegebenenfalls mit Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position am Phenylring, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Diniedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)phenylpiperazinoresten oder -COD' substituiert sein kann, worin D' ein (C_1-C_4)-Alkoxy-, Hydroxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Diniedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazino-, (C_3-C_8)-Cycloalkyl- oder Phenyl- oder Naphthylrest ist, der mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, N-Niedrig(C_1-C4)alkylamino-, N,N-Di-nied-

rig(C_1-C_4)-alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)-phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position des Phenylrings substituiert sein können, oder einer Gruppe der Formel -COD' substituiert sein kann, worin D' ein Hydroxy-, (C_1-C_4)-Alkoxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist; und R^5 ein Carboxyl- oder Tetrazolylrest ist oder ein pharmazeutisch annehmbares Salz davon.

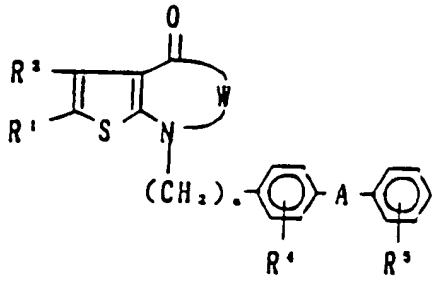
11. Verbindung nach Anspruch 1 oder pharmazeutisch annehmbares Salz davon, die ausgewählt ist aus der Gruppe bestehend aus Ethyl-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-5-carboxylat, 2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-5-carbonsäure, Methoxyethyl-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-5-carboxylat, 2-Ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-4(7H)-on, 2-Ethyl-5-(N-phenylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-4(7H)-on und 2-Ethyl-5-(N-2-pyridylmethylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-4(7H)-on.

12. Verbindung nach Anspruch 10, worin R^1 ein Ethylrest ist, R^5 ein 1H-Tetrazol-5-yl-rest ist und R^7 ein Butyl-, Benzyl-, Ethyl-, p-Fluorphenyl-, 2,5-Dichlorphenyl-, Cyclohexyl-, Ethoxycarbonylmethyl- oder 2-[4-(o-Methoxyphenyl)-piperazino]ethylrest ist.

13. Pharmazeutische Zusammensetzung zur Antagonisierung von Angiotensin-II umfassend eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon in Mischung mit einem pharmazeutisch annehmbaren Träger, Hilfsstoff oder Verdünnungsmittel.

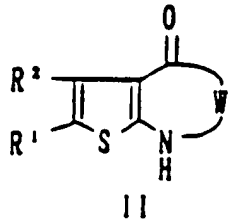
14. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes davon zur Herstellung eines Arzneimittels, um Angiotensin-II zu antagonisieren.

15. Verfahren zur Herstellung einer Verbindung der Formel (I):



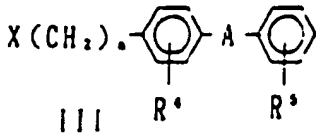
(I)

worin W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, A und n die in Anspruch 1 definierten Bedeutungen haben oder eines pharmazeutisch annehmbaren Salzes davon, umfassend, daß man eine Verbindung der Formel (II):



II

worin R^1, R^2 und W die oben angegebenen Bedeutungen haben mit einer Verbindung der Formel (III):

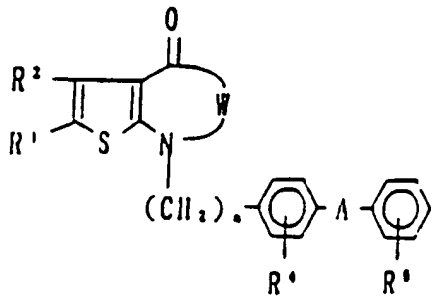


III

worin R^4, R^5, A und n die oben angegebenen Bedeutungen haben und X Halogen ist, umsetzt und (i) falls erwünscht, eine Verbindung der Formel (I) worin R^5 ein Cyanorest oder ein geschützter Tetrazolylrest ist und R^1, R^2, R^4, R^5, A, W und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^5 ein Tetrazolylrest ist und R^1, R^2, R^4, R^5, A, W und n die oben angegebenen Bedeutungen haben, (ii) falls erwünscht, eine Verbindung der Formel (I), worin $-R^3$ ein Niedrig(C_1-C_4)alkylcarbonyl- oder Halogencarbonylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^3 ein Carboxylrest oder ein gegebenenfalls substituierter Carbamoylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben oder (iii) falls erwünscht, eine Verbindung der Formel (I), worin $-R^3$ ein Carboxylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^3 ein Halogencarbonylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben und, falls erwünscht, eine Verbindung der Formel (I) in ein pharmazeutisch annehmbares Salz davon umwandelt.

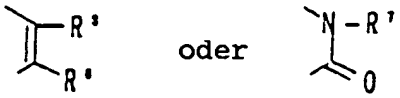
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



(I)

worin W



ist,
R^1 und R^2, die gleich oder verschieden sein können, jeweils unabhängig

(1) Wasserstoff,
(2) Halogen,
(3) Cyanoreste,
(4) Nitroreste,
(5) Gruppen der Formel R^8CONH-, worin R^8 Wasserstoff oder eine (C_1-C_8)-Alkylgruppe ist, die mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Ben-

zylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position an dem Phenylring substituiert sein können, oder Naphthylresten substituiert sein kann oder

(6) Kohlenwasserstoffreste sind, ausgewählt aus der Gruppe bestehend aus (i) (C_1-C_8)-Alkylresten, (ii) (C_2-C_8)-Alkenylresten, (iii) (C_2-C_8)Alkinylresten, (iv) (C_3-C_8)-Cycloalkylresten, (v) einem aromatischen Kohlenwasserstoff ausgewählt aus der Gruppe bestehend aus Phenyl- und Naphthylresten, wobei der Kohlenwasserstoffrest mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)-alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position am Phenylring substituiert sein können, oder einer Gruppe der Formel -COD' substituiert sein kann, worin D' ein Hydroxy-, (C_1-C_4)-Alkoxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist;

R^3 (1) Wasserstoff,
(2) ein (C_1-C_8)-Alkyl- oder (C_2-C_8)-Alkenylrest, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Halogen-, Niedrig(C_1-C_4)alkoxyresten oder -COD" substituiert sein kann, worin D" ein Niedrig(C_1-C_4)alkoxy-, Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist oder
(3) -COD ist, worin D Wasserstoff, ein (C_1-C_4)-Alkoxy-, Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-(p-Fluorphenyl)piperazino- oder N-Phenylpiperazinorest ist, worin die Alkyl-, Aryl- und Heteroarylgruppen gegebenenfalls mit Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sek.-Butyl-, Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)-alkylamino-, Morpholino-, Piperidino-, Piperazino-, n-Phenylpiperazino-, Halogen-, Nitro- oder Niedrig-(C_1-C_4)alkoxyresten substituiert sein können;

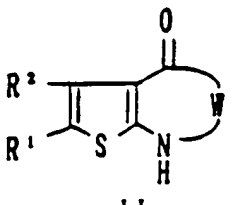
R^4 Wasserstoff, Halogen oder ein Nitrorest ist;

R^5 ein Carboxyl-, Niedrig(C_1-C_4)alkoxycarbonyl-, Cyano-, Tetrazolyl-, Trifluormethansulfonsäureamid-, Phosphorsäure- oder Sulfonsäurerest ist;

R^6 Wasserstoff oder ein (C_1-C_8)-Alkyl- oder (C_2-C_8)-Alkenylrest ist, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Halogen-, Niedrig(C_1-C_4)alkoxyresten oder -COD" substituiert sein kann, worin D" ein Niedrig(C_1-C_4)alkoxy-, Hydroxy-, Halogen-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist;

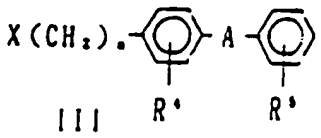
R^7 ein Kohlenwasserstoffrest ist, der wie R^1 und R^2 substituiert sein kann; A eine direkte Bindung oder ein Abstandshalter mit einer Atomlänge von 2 oder weniger zwischen der Phenylengruppe und der Phenylgruppe ist ausgewählt aus der Gruppe bestehend aus einem (C_1-C_4)-Alkylenrest, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2- oder -CH=CH- und n eine ganze Zahl von 1 oder 2 ist

und eines pharmazeutisch annehmbaren Salzes davon umfassend, daß man eine Verbindung der Formel (II):



II

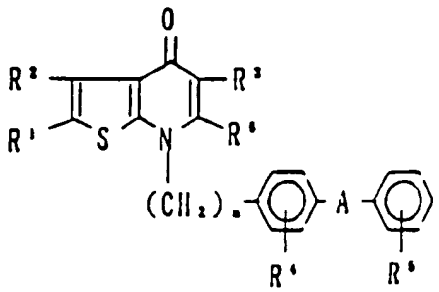
worin R^1, R^2 und W die oben angegebenen Bedeutungen haben mit einer Verbindung der Formel (III):



III

worin R^4, R^5, A und n die oben angegebenen Bedeutungen haben und X Halogen ist, umsetzt und (i) falls erwünscht, eine Verbindung der Formel (I) worin R^5 ein Cyanorest oder ein geschützter Tetrazolylrest ist und R^1, R^2, R^4, R^5, A, W und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^5 ein Tetrazolylrest ist und R^1, R^2, R^4, R^5, A, W und n die oben angegebenen Bedeutungen haben, (ii) falls erwünscht, eine Verbindung der Formel (I), worin $-R^3$ ein Niedrig(C_1-C_4)alkylcarbonyl- oder Halogencarbonylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^3 ein Carboxylrest oder ein gegebenenfalls substituierter Carbamoylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben oder (iii) falls erwünscht, eine Verbindung der Formel (I), worin $-R^3$ ein Carboxylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben, in eine Verbindung der Formel (I) umwandelt, worin R^3 ein Halogencarbonylrest ist und R^1, R^2, R^4, R^5, R^6, A und n die oben angegebenen Bedeutungen haben und, falls erwünscht, eine Verbindung der Formel (I) in ein pharmazeutisch annehmbares Salz davon umwandelt.

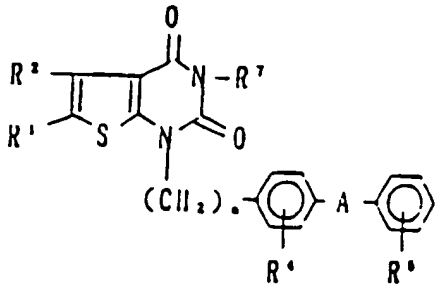
2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (Ia):



(Ia)

worin R^1 und R^2 wie in Anspruch 1 definiert sind;
R^3 Wasserstoff, ein Formylrest, ein gegebenenfalls substituierter Alkyl- oder Alkenylrest, wie in Anspruch 1 definiert, ist oder -COD ist, worin D ein Alkoxy-, Hydroxy-, Halogen- oder gegebenenfalls substituierter Aminorest ist, wie in Anspruch 1 definiert;
R^4 Wasserstoff, Halogen oder ein Nitrorest ist;
R^5 wie in Anspruch 1 definiert ist;
R^6, A und n wie in Anspruch 1 definiert sind und eines pharmazeutisch annehmbaren Salzes davon.

3. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (Ib):



(Ib)

worin R^1 und R^2 wie in Anspruch 1 definiert sind;
R^4 Wasserstoff, Halogen oder ein Nitrorest ist;
R^5 wie in Anspruch 1 definiert ist;
R^7, A und n wie in Anspruch 1 definiert sind und eines pharmazeutisch annehmbaren Salzes davon.

4. Verfahren nach Anspruch 1, worin ein wie für die Substituenten des Kohlenwasserstoffrestes in Anspruch 1 definierter gegebenenfalls substituierter Aminorest ein Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Benzylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino- oder N-(m-Methoxy)-phenylpiperazinorest ist.

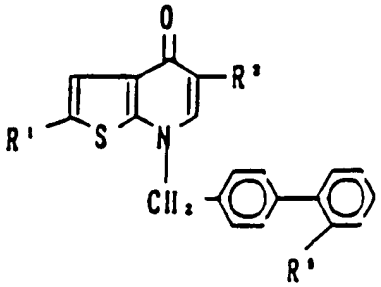
5. Verfahren nach Anspruch 1, worin D' ein Amino-, Methylamino-, Dimethylamino-, Phenylamino-, Benzylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist.

6. Verfahren nach Anspruch 1, worin D ein Amino-, N-(C_1-C_4)Alkylamino-, N,N-Di(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-Phenylpiperazino- oder N-(p-Fluorphenyl)piperazinorest ist, worin die Alkyl-, Aryl- und Heteroarylgruppen gegebenenfalls mit Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, sek.-Butyl-, Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, Halogen-, Nitro- oder Niedrig(C_1-C_4)alkoxyresten substituiert sein können.

7. Verfahren nach Anspruch 1, worin R^5 ein Tetrazolylrest ist.

8. Verfahren nach Anspruch 1, worin R^5 in ortho-Position ist.

9. Verfahren nach Anspruch 1, zur Herstellung einer Verbindung der Formel (Ia'):



(Ia')

worin R^1 ein (C_1-C_8)-Alkylrest ist;
R^3

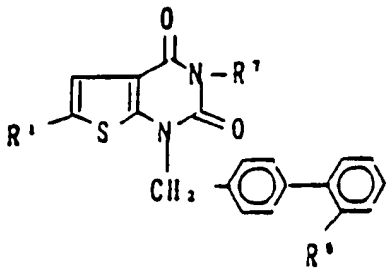
(1) Wasserstoff,

(2) ein (C_1-C_8)-Alkylrest ist, der geradkettig oder verzweigt sein kann und gegebenenfalls mit Hydroxyl-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Diniedrig(C_1-C_4)alkylamino-, Halogen-, (C_1-C_4)-Alkoxyresten oder -COD" substituiert sein kann, worin D" ein (C_1-C_4)-Alkoxy-, Hydroxy-, Halogen-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist oder

(3) -COD ist, worin D Wasserstoff, ein (C_1-C_4)-Alkoxy-, Hydroxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Benzylamino-, Naphthylmethylamino-, Pyridylamino-, Pyridylmethylamino-, Morpholino-, Piperidino-, Piperazino-, Piperidylmethyl-, N-(p-Fluorphenyl)piperazino- oder N-Phenylpiperazinorest ist und R^5 ein Carboxyl- oder Tetrazolylrest ist oder

eines pharmazeutisch annehmbaren Salzes davon.

10. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (Ib'):



(Ib')

worin R^1 ein (C_1-C_8)-Alkylrest ist; R^7 ein (C_1-C_8)-Alkylrest ist, der gegebenenfalls mit Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position am Phenylring substituiert sein können, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Diniedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)phenylpiperazinoresten oder -COD' substituiert sein kann, worin D' ein (C_1-C_4)-Alkoxy-, Hydroxy-, Amino-, N-Niedrig(C_1-C_4)alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazino-, (C_3-C_8)-Cycloalkyl- oder Phenyl- oder Naphthylrest ist, der mit Hydroxyl-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkyl-, Halogen-, Nitro-, Amino-, N-Niedrig(C_1-C4)alkylamino-, N,N-Diniedrig(C_1-C_4)-alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino-, N-Phenylpiperazino-, N-(m-Methoxy)phenylpiperazino-, (C_1-C_4)-Alkanoyloxy-, Benzoyloxy-, Phenylresten, die mit Halogen-, Nitro-, (C_1-C_4)-Alkoxy-, (C_1-C_4)-Alkylresten an freigewählter Position des Phenylrings substituiert sein können, oder einer Gruppe der Formel -COD' substituiert sein kann, worin D' ein Hydroxy-, (C_1-C_4)-Alkoxy-, Amino-, N-Niedrig(C_1-C_4)-alkylamino-, N,N-Di-niedrig(C_1-C_4)alkylamino-, Phenylamino-, Naphthylamino-, Benzylamino-, Naphthylmethylamino-, Morpholino-, Piperidino-, Piperazino- oder N-Phenylpiperazinorest ist; und R^5 ein Carboxyl- oder Tetrazolylrest ist oder eines pharmazeutisch annehmbaren Salzes davon.

11. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, die ausgewählt ist aus der Gruppe bestehend aus Ethyl-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-5-carboxylat, 2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-5-carbonsäure, Methoxyethyl-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]-pyridin-5-carboxylat, 2-Ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-4(7H)-on, 2-Ethyl-5-(N-phenylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihydrothieno[2,3-b]pyridin-4(7H)-on und 2-Ethyl-5-(N-2-pyridylmethylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-4,7-Dihy drothieno[2,3-b]pyridin-4(7H)-on, oder eines pharmazeutisch annehmbaren Salzes davon.

12. Verfahren nach Anspruch 10, worin R^1 ein Ethylrest ist, R^5 ein 1H-Tetrazol-5-yl-rest ist und R^7 ein Butyl-, Benzyl-, Ethyl-, p-Fluorphenyl-, 2,5-Dichlorphenyl-, Cyclohexyl-, Ethoxycarbonylmethyl- oder 2-[4-(o-Methoxyphenyl)-piperazino]ethylrest ist.

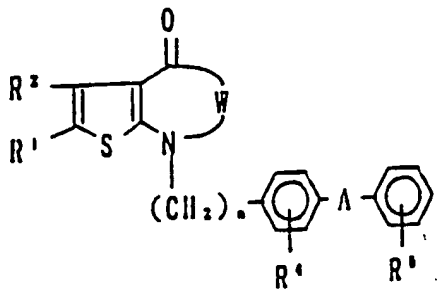
13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, um Angiotensin-II zu antagonisieren, das umfaßt, daß man eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon mit einem pharmazeutisch annehmbaren Träger, Hilfsstoff oder Verdünnungsmittel vermischt.

14. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes davon zur Herstellung eines Arzneimittels, um Angiotensin-II zu antagonisieren.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule

(I) 

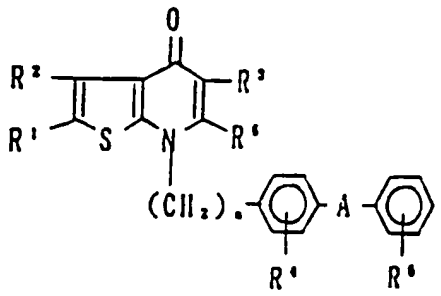
dans laquelle W est un groupe

R^1 et R^2, identiques ou différents, représentent chacun indépendamment (1) un atome d'hydrogène, (2) un atome d'halogène, (3) un groupe cyano, (4) un groupe nitro, (5) un groupe de formule R^8CO-NH-, où R^8 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} pouvant être substitué par un groupe hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, un atome d'halogène, un groupe nitro, amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant porter un substituant halogéno, nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe naphtyle, ou (6) un résidu hydrocarboné choisi dans le groupe formé par (i) un groupe alkyle en C_{1-8}, (ii) alcényle en C_{2-8}, (iii) alcynyle en C_{2-8}, (iv) cycloalkyle en C_{3-8}, (v) un résidu hydrocarboné aromatique choisi dans le groupe formé par les résidus phényle et naphtyle, ledit résidu hydrocarboné pouvant être substitué par un résidu hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, halogéno, nitro, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, N-(m-méthoxy)phénypipérazino, alcanoyloxy en C_{1-4},benzoyloxy, phényle pouvant porter un substituant halogéno, nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe de formule -COD', où D' représente un groupe hydroxy, alcoxy en C_{1-4}, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;
R^3 représente (1) un atome d'hydrogène, (2) un groupe alkyle en C_{1-8} ou alcényle en C_{2-8},linéaires ou ramifiés et qui peuvent être subsitués par un groupe hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy en C_{1-4}, ou un groupe de formule -COD", où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino; ou (3) un groupe -COD où D représente un atome d'hydrogène, un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-(p-fluorophényl)pipérazino ou N-phénylpipérazino, lesdits

groupes alkyle, aryle et hétéroaryle pouvant être substitué par un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, sec-butyle, hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, halogéno, nitro ou alcoxy en C_{1-4};
R^4 est un atome d'hydrogène, d'halogène ou un groupe nitro, R^5 est un groupe carboxyle, (alcoxy en C_{1-4})-carbonyle, cyano, tétrazolyle, acide trifluorométhanesulfonique, acide phosphorique ou acide sulfonique,
R^6 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} ou alcényle en C_{2-8} à chaîne linéaire ou ramifiée et pouvant être substitué par un groupe hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy inférieur en C_{1-4} ou un groupe - COD" où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;
R^7 représente un résidu hydrocarboné pouvant être substitué comme R^1 et R^2; A est une liaison directe ou un bras de liaison long de 2 atomes ou moins entre le groupe phénylène et le groupe phényle, choisi dans le groupe formé par les résidus alkylène en C_{1-4}, -C(=O)-,-O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2- ou -CH=CH-,et n est un nombre entier égal a 1 ou 2;
et un sel pharmacologiquement acceptable d'un tel composé.

2. Composé conforme à la revendication 1 qui est un composé de formule (Ia) :

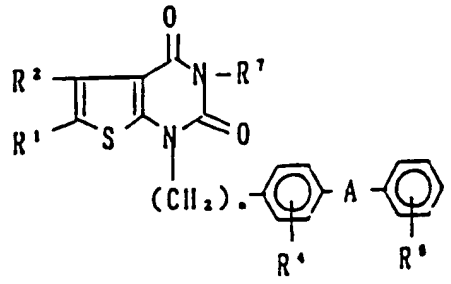
(Ia)



dans laquelle R^1 et R^2 sont définis comme dans la revendication 1,
R^3 représente un atome d'hydrogène, un groupe formyle, un groupe alkyle ou alcényle éventuellement substitués, définis dans la revendication 1, ou un groupe-COD où D représente un groupe alcoxy, hydroxy, halogéno ou amino éventuellement substitué de la manière définie dans la revendication 1;
R^4 représente un atome d'hydrogène ou d'halogène ou un groupe nitro;
R^5 est défini comme dans la revendication 1;
R^6, A et n sont définis comme dans la revendication 1; et un sel pharmacologiquement acceptable d'un tel composé.

3. Composé conforme à la revendication 1 qui est un composé de formule (Ib)

(Ib)



dans laquelle R^1 et R^2 sont définis comme dans la revendication 1;
R^4 représente un atome d'hydrogène ou d'halogène ou un groupe nitro; R^5 est défini comme dans la revendication 1;
R^7, A et n sont définis comme dans la revendication 1;
et un sel pharmacologiquement acceptable d'un tel composé.

4. Composé conforme à la revendication 1 dans lequel un groupe amino éventuellement substitué défini dans la revendication 1 pour les substituants dudit résidu hydrocarboné est un groupe amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino ou N-(m-méthoxy)phénylpipérazino.

5. Composé conforme à la revendication 1 dans lequel ledit résidu D' est un résidu amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino.

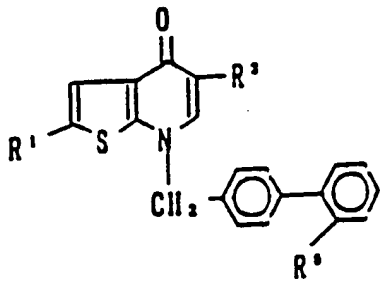
6. Composé conforme à la revendication 1 dans lequel ledit résidu D est un groupe amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-phénylpipérazino ou N-(p-fluorophényl)pipérazino où lesdits groupes alkyle, aryle et hétéroaryle peuvent être substitués par un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, sec-butyle, hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N-N-di(alkyle en C_{1-4})-amino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, halogéno, nitro ou alcoxy en C_{1-4}.

7. Composé conforme à la revendication 1 dans lequel ledit groupe R^5 est un résidu tétrazolyle.

8. Composé conforme à la revendication 1 dans lequel ledit résidu R^5 est en position ortho.

9. Composé conforme à la revendication 1 qui est un composé de formule (Ia') :

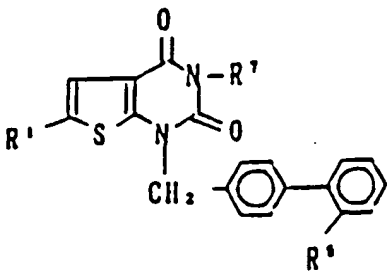
(Ia')



dans laquelle R^1 est un groupe alkyle en C_{1-8}, R^3 est (1) un atome d'hydrogène, (2) un groupe alkyle en C_{1-8}, linéaire ou ramifié, pouvant être substitué par un groupe hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy en C_{1-4}, ou un groupe -COD" où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino; ou (3) un groupe -COD où D représente un atome d'hydrogène, un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-(p-fluorophényl)pipérazino ou N-phénylpipérazino, et
R^5 est un groupe carboxyle ou tétrazolyle,
ou un sel pharmaceutiquement acceptable d'un tel composé.

10. Composé conforme à la revendication 1 qui est un composé de formule (Ib') :

(Ib')



dans laquelle R^1 est un groupe alkyle en C_{1-8}, R^7 est un groupe alkyle en C_{1-8} pouvant être substitué par un groupe phényle qui, à son tour peut être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4}, alkyle en C_{1-4}

en une position choisie du noyau phényle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino, N-(m-méthoxy)phénylpipérazino, ou un groupe -COD' où D' représente un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, cycloalkyle en C_{3-8}, ou phényle ou naphtyle pouvant être substitué par un groupe hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, halogéno, nitro, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, N-(m-méthoxy)phénylpipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe de formule -COD' où D' représente un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;
R^5 est un groupe carboxyle ou tétrazolyle
ou un sel pharmacologiquement acceptable d'un tel composé.

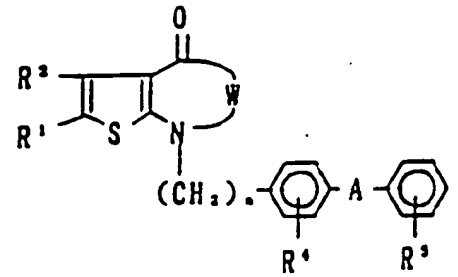
11. Composé conforme à la revendication 1 ou un sel pharmaceutiquement acceptable d'un tel composé, qui est choisi dans le groupe formé par
le 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylate d'éthyle,
l'acide 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylique,
le 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylate de méthoxyéthyle, la 2-éthyl-5-(N-benzylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridin-4(7H)-one,
la 2-éthyl-5-(N-phénylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-4(7H)-one, et
la 2-éthyl-5-(N-2-pyridylméthylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]-pyridin4(7H)-one.

12. Composé conforme à la revendication 10 dans lequel R^1 est un groupe éthyle, R^5 un groupe 1H-tétrazol-5-yle et R^7 est un groupe butyle, benzyle, éthyle, p-fluorophényle, 2,5-dichlorophényle, cyclohexyle, éthoxycarbonylméthyle ou 2-[4-(o-méthoxyphényl)-pipérazino]éthyle.

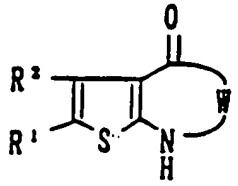
13. Composition pharmaceutique à effet antagoniste de l'angiotensine II comprenant une quantité thérapeutiquement efficace d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé mélangé avec un véhicule, excipient ou diluant pharmaceutiquement acceptables.

14. Utilisation d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament à effet antagoniste de l'angiotensine II.

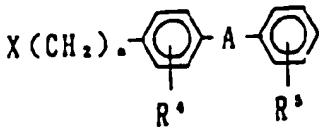
15. Procédé de préparation d'un composé de formule (I)

(I) 

dans laquelle W, R^1, R^2, R^3, R^4, R^5, R^6, R^7, A et n ont la signification indiquée dans la revendication 1, ou d'un sel pharmaceutiquement acceptable d'un tel composé,
lequel procédé consiste à faire réagir un composé de formule (II)

(II) 

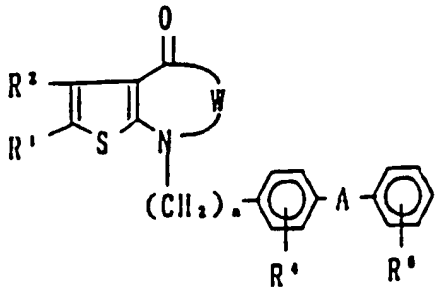
dans laquelle R^1, R^2 et W ont les significations indiquées ci-dessus, avec un composé de formule (III)

(III) 

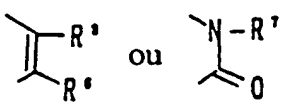
dans laquelle R^4, R^5, A et n ont les significations indiquées ci-dessus, et X est un atome d'halogène, et, (i) si on le souhaite, à convenir un composé de formule (I) où R^5 est un groupe cyano ou un groupe tétrazolyle protégé, et R^1, R^2, R^4, R^5, A, W et n ont la signification indiquée ci-dessus, en un composé de formule (I) où R^5 représente un groupe tétrazolyle et R^1, R^2, R^4, R^5, A, W et n ont la signification indiquée ci-dessus, (ii) si on le souhaite, à convertir un composé de formule (I) où -R^3 est un groupe alcoxycarbonyle en C_{1-4} ou halogénocarbonyle, et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, en un composé de formule (I) où -R^3 est un groupe carboxyle ou carbamoyle éventuellement substitué, et R^1, R^2, R^3, R^4, R^5, R^6, R^7, A et n ont la signification ci-dessus, ou (iii) si on le souhaite, à convertir d'un composé de formule (I) où R^3 est un groupe carboxyle et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, en un composé de formule (I) dans laquelle R^3 est un résidu halogénocarbonyle et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, et si on le souhaite, à convertir un composé de formule (I) en un sel pharmaceutiquement acceptable.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule

(I) 

dans laquelle W est un groupe



R^1 et R^2, identiques ou différents, représentent chacun indépendamment (1) un atome d'hydrogène, (2) un atome d'halogène, (3) un groupe cyano, (4) un groupe nitro, (5) un groupe de formule R^8CO-NH-, où R^8 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} pouvant être substitué par un groupe hydroxyle, alcoxy en C_{1-4},

alkyle en C_{1-4}, un atome d'halogène, un groupe nitro, amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant porter un substituant halogéno, nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe naphtyle, ou (6) un résidu hydrocarboné choisi dans le groupe formé par (i) un groupe alkyle en C_{1-8}, (ii) alcényle en C_{2-8}, (iii) alcynyle en C_{2-8}, (iv) cycloalkyle en C_{3-8}, (v) un résidu hydrocarboné aromatique choisi dans le groupe formé par les résidus phényle et naphtyle, ledit résidu hydrocarboné pouvant être substitué par un résidu hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, halogéno, nitro, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, N-(m-méthoxy)phénypipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant porter un substituant halogéno, nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe de formule -COD', où D' représente un groupe hydroxy, alcoxy en C_{1-4}, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;

R^3 représente (1) un atome d'hydrogène, (2) un groupe alkyle en C_{1-8} ou alcényle en C_{2-8}, linéaires ou ramifiés et qui peuvent être substitués par un groupe hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy en C_{1-4}, ou un groupe de formule -COD", où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino; ou (3) un groupe -COD où D représente un atome d'hydrogène, un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-(p-fluorophényl)pipérazino ou N-phénylpipérazino, lesdits groupes alkyle, aryle et hétéroaryle pouvant être substitué par un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, sec-butyle, hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, halogéno, nitro ou alcoxy en C_{1-4};

R^4 est un atome d'hydrogène, d'halogène ou un groupe nitro,

R^5 est un groupe carboxyle, (alcoxy en C_{1-4})-carbonyle, cyano, tétrazolyle, acide trifluorométhanesulfonique, acide phosphorique ou acide sulfonique,

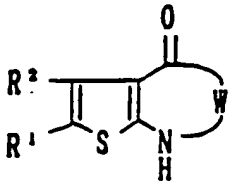
R^6 représente un atome d'hydrogène ou un groupe alkyle en C_{1-8} ou alcényle en C_{2-8} à chaîne linéaire ou ramifiée et pouvant être substitué par un groupe hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy inférieur en C_{1-4} ou un groupe - COD" où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;

R^7 représente un résidu hydrocarboné pouvant être substitué comme R^1 et R^2; A est une liaison directe ou un bras de liaison long de 2 atomes ou moins entre le groupe phénylène et le groupe phényle, choisi dans le groupe formé par les résidus alkylène en C_{1-4}, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, -O-CH_2-, -S-CH_2- ou -CH=CH-, et n est un nombre entier égal a 1 ou 2;

et un sel pharmacologiquement acceptable d'un tel composé,

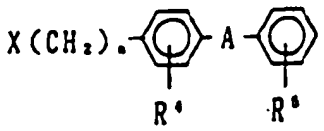
lequel procédé consiste à faire réagir un composé de formule (II)

(II)



dans laquelle R^1, R^2 et W ont les significations indiquées ci-dessus, avec un composé de formule (III)

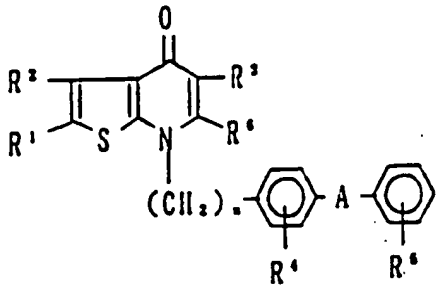
(III)



dans laquelle R^4, R^5, A et n ont les significations indiquées ci-dessus, et X est un atome d'halogène, et, (i) si on le souhaite, à convertir un composé de formule (I) où R^5 est un groupe cyano ou un groupe tétrazolyle protégé, et R^1, R^2, R^4, R^5, A, W et n ont la signification indiquée ci-dessus, en un composé de formule (I) où R^5 représente un groupe tétrazolyle et R^1, R^2, R^4, R^5, A, W et n ont la signification indiquée ci-dessus, (ii) si on le souhaite, à convertir un composé de formule (I) où -R^3 est un groupe alcoxycarbonyle en C_{1-4} ou halogénocarbonyle, et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, en un composé de formule (I) où -R^3 est un groupe carboxyle ou carbamoyle éventuellement substitué, et R^1, R^2, R^3, R^4, R^5, R^6, R^7, A et n ont la signification ci-dessus, ou (iii) si on le souhaite, à convertir d'un composé de formule (I) où R^3 est un groupe carboxyle et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, en un composé de formule (I) dans laquelle R^3 est un résidu halogénocarbonyle et R^1, R^2, R^4, R^5, R^6, A et n ont la signification indiquée ci-dessus, et si on le souhaite, à convertir un composé de formule (I) en un sel pharmaceutiquement acceptable.

2. Procédé conforme à la revendication 1 pour la préparation d'un composé de formule (Ia) :

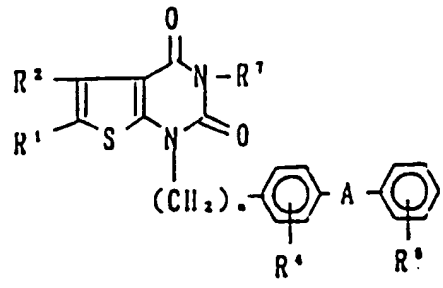
(Ia)



dans laquelle R^1 et R^2 sont définis comme dans la revendication 1,
R^3 représente un atome d'hydrogène, un groupe formyle, un groupe alkyle ou alcényle éventuellement substitués, définis dans la revendication 1, ou un groupe-COD où D représente un groupe alcoxy, hydroxy, halogéno ou amino éventuellement substitué de la manière définie dans la revendication 1;
R^4 représente un atome d'hydrogène ou d'halogène ou un groupe nitro;
R^5 est défini comme dans la revendication 1;
R^6, A et n sont définis comme dans la revendication 1;
et d'un sel pharmacologiquement acceptable d'un tel composé.

3. Procédé conforme à la revendication 1 pour la préparation d'un composé de formule (Ib)

(Ib)



dans laquelle R^1 et R^2 sont définis comme dans la revendication 1; R^4 représente un atome d'hydrogène ou d'halogène ou un groupe nitro; R^5 est défini comme dans la revendication 1;
R^7, A et n sont définis comme dans la revendication 1;
et d'un sel pharmacologiquement acceptable d'un tel composé.

4. Procédé conforme à la revendication 1 dans lequel un groupe amino éventuellement substitué défini dans la revendication 1 pour les substituants dudit résidu hydrocarboné est un groupe amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino, N-phénylpipérazino ou N-(m-méthoxy)phénylpipérazino.

5. Procédé conforme à la revendication 1 dans lequel ledit résidu D' est un résidu amino, méthylamino, diméthylamino, phénylamino, benzylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino.

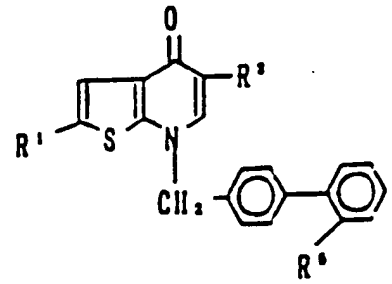
6. Procédé conforme à la revendication 1 dans lequel ledit résidu D est un groupe amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-phénylpipérazino ou N-(p-fluorophényl)pipérazino où lesdits groupes alkyle, aryle et hétéroaryle peuvent être substitués par un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, sec-butyle, hydroxyle, amino, N-(alkyle en C_{1-4})-amino, N-N-di(alkyle en C_{1-4})-amino, morpholino, pipéridino, pipérazino, N-phénylpipérazino, halogéno, nitro ou alcoxy en C_{1-4}.

7. Procédé conforme à la revendication 1 dans lequel ledit groupe R^5 est un résidu tétrazolyle.

8. Procédé conforme à la revendication 1 dans lequel ledit résidu R^5 est en position ortho.

9. Procédé conforme à la revendication 1 pour la préparation d'un composé de formule (Ia') :

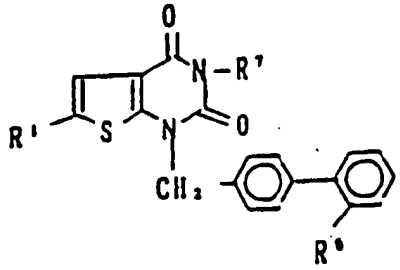
(Ia')



dans laquelle R^1 est un groupe alkyle en C_{1-8},
R^3 est (1) un atome d'hydrogène, (2) un groupe alkyle en C_{1-8}, linéaire ou ramifié, pouvant être substitué par un groupe hydroxyle, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, halogéno, alcoxy en C_{1-4}, ou un groupe -COD" où D" représente un groupe alcoxy en C_{1-4}, hydroxy, halogéno, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino; ou
(3) un groupe -COD où D représente un atome d'hydrogène, un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, benzylamino, naphtylméthylamino, pyridylamino, pyridylméthylamino, morpholino, pipéridino, pipérazino, pipéridylméthyle, N-(p-fluorophényl)pipérazino ou N-phénylpipérazino, et
R^5 est un groupe carboxyle ou tétrazolyle, ou d'un sel pharmaceutiquement acceptable d'un tel composé.

10. Procédé conforme à la revendication 1 pour la préparation d'un composé de formule (Ib') :

(Ib')



dans laquelle R^1 est un groupe alkyle en C_{1-8}, R^7 est un groupe alkyle en C_{1-8} pouvant être substitué par un groupe phényle qui, à son tour peut être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino, N(m-méthoxy)phénylpipérazino, ou un groupe -COD' où D' représente un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-

amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, cycloalkyle en C_{3-8}, ou phényle ou naphtyle pouvant être substitué par un groupe hydroxyle, alcoxy en C_{1-4}, alkyle en C_{1-4}, halogéno, nitro, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino, N-(m-méthoxy)phénylpipérazino, alcanoyloxy en C_{1-4}, benzoyloxy, phényle pouvant être substitué par un atome d'halogène, un groupe nitro, alcoxy en C_{1-4}, alkyle en C_{1-4} en une position choisie du noyau phényle, ou un groupe de formule -COD' où D' représente un groupe alcoxy en C_{1-4}, hydroxy, amino, N-(alkyle en C_{1-4})-amino, N,N-di(alkyle en C_{1-4})-amino, phénylamino, naphtylamino, benzylamino, naphtylméthylamino, morpholino, pipéridino, pipérazino ou N-phénylpipérazino;

R^5 est un groupe carboxyle ou tétrazolyle

ou d'un sel pharmacologiquement acceptable d'un tel composé.

11. Procédé conforme à la revendication 1 pour la préparation d'un composé choisi dans le groupe formé par le 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylate d'éthyle,
l'acide 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylique,
le 2-éthyl-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-5-carboxylate de méthoxyéthyle,
la 2-éthyl-5-(N-benzylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridin-4(7H)-one,
la 2-éthyl-5-(N-phénylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]pyridine-4(7H)-one, et
la 2-éthyl-5-(N-2-pyridylméthylcarbamoyl)-7-{[2'-(1H-tétrazol-5-yl)biphényl-4-yl]méthyl]-4-oxo-4,7-dihydrothiéno[2,3-b]-pyridin4(7H)-one.

12. Procédé conforme à la revendication 10 dans lequel R^1 est un groupe éthyle, R^5 un groupe 1H-tétrazol-5-yle et R^7 est un groupe butyle, benzyle, éthyle, p-fluorophényle, 2,5-dichlorophényle, cyclohexyle, éthoxycarbonylméthyle ou 2-[4-(o-méthoxyphényl)-pipérazino]éthyle.

13. Procédé de préparation d'une composition pharmaceutique à effet antagoniste de l'angiotensine II comprenant la mélangeage d'une quantité thérapeutiquement efficace d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé avec un véhicule, excipient ou diluant pharmaceutiquement acceptables.

14. Utilisation d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé pour la fabrication d'un médicament à effet antagoniste de l'angiotensine II.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 443 568 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **91102513.8**

(22) Date of filing: **21.02.91**

(51) Int. Cl.5: **C07D 495/04**, A61K 31/435, //(C07D495/04,333:00,221:00), (C07D495/04,333:00,239:00)

(30) Priority: **22.02.90 JP 42125/90**
17.01.91 JP 3958/91

(43) Date of publication of application:
28.08.91 Bulletin 91/35

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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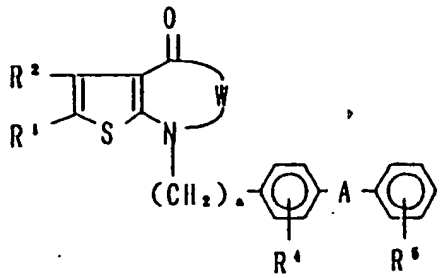
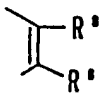
(54) Fused thiophene derivatives, their production and use.

(57) Novel fused thiophene derivatives of the formula (I):



(I)

wherein W is



or

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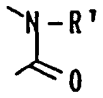


R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted; R^3 is hydrogen, optionally substituted alkyl or alkenyl, or -COD wherein D is hydrogen, alkoxy, hydroxy, halogen, or optionally substituted amino; R^4 is hydrogen, halogen or nitro; R^6 is a residue capable of forming an anion or a residue convertible into an anion; R^5 is hydrogen or optionally substituted alkyl or alkenyl; R^7 is a hydrocarbon residue which may be substituted; A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2; and the pharmaceutically acceptable salts thereof have potent angiotensin II antagonist activity and antihypertensive activity, thus being useful as therapeutic agents for treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc.

FIELD OF THE INVENTION

The present invention relates to novel fused thiophene derivatives having potent pharmacological activity and intermediates for the preparation thereof. More particularly, the present invention relates to compounds having potent angiotensin II antagonist activity and antihypertensive activity, which are useful as therapeutic agents for treating circulatory diseases such as hypertensive diseases, heart diseases, strokes, etc.

BACKGROUND OF THE INVENTION

The renin-angiotensin system is involved in the homeostatic function to control systemic blood pressure, the volume of body fluid, balance among the electrolytes, etc., associated with the aldosterone system. Development of angiotensin II converting enzyme inhibitors (ACE inhibitor) (this converting enzyme produces angiotensin II which possesses strong vasoconstrictive activity) has clarified the relation between the renin-angiotensin system and hypertension. Since angiotensin II elevates blood pressure via the angiotensin II receptors on cell membranes, angiotensin II antagonists as well as the ACE inhibitor would be useful in treating hypertension.

It has been reported that various angiotensin II analogues such as saralasin, [Sar^1,Ile^8]A II, and the like, possess potent angiotensin II antagonist activity.

It has, however, been reported that, when peptide antagonists are administered parenterally, their actions are not prolonged and, when administered orally, they are ineffective (M. A. Ondetti and D. W. Cushman, Annual Reports in Medicinal Chemistry, 13, 82-91 (1978)).

Non-peptide angiotensin II antagonists are disclosed in Japanese Patent Laid Open No. 71073/1981; No. 71074/1981; No. 92270/1982; No. 157768/1983; No. 240683/1987; No. 23868/1988; and No. 117876/1989, and European Patent Laid Open No. 0323841, etc.

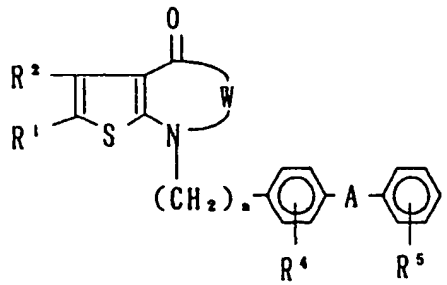
Imidazole derivatives having angiotensin II antagonist activity are disclosed in A. T. Chiu et al., Eur. J. Pharm., 157, 13 (1981), P. C. Wong et al., J. Pharmcol. Exp. Ther., 247, 1 (1988), P. C. Wong et al., Hypertension, 13, 489 (1989), etc.

It has not yet been known that fused thiophene derivatives possess potent angiotensin II antagonist activity.

SUMMARY OF THE INVENTION

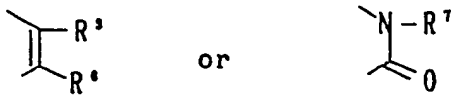
The present inventors made extensive investigations to prepare useful compounds which have angiotensin II antagonist activity. As a result of these researches, the present inventors have succeeded in synthesizing fused thiophene derivatives possessing excellently potent angiotensin II antagonist activity and developed their work to accomplish the present invention.

The present invention provides fused thiophene derivatives having the formula I:



(I)

wherein W is



R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^3 is hydrogen, optionally substituted alkyl or alkenyl, or -COD wherein D is hydrogen, alkoxy, hydroxy, halogen, or optionally substituted amino;
R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^6 is hydrogen or optionally substituted alkyl or alkenyl;
R^7 is a hydrocarbon residue which may be substituted;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2;
and the pharmaceutically acceptable salts thereof.

These compounds are potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the fused thiophene derivative having the formula I and a pharmaceutically acceptable carrier useful in treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, etc., and processes for preparing such compounds and compositions.

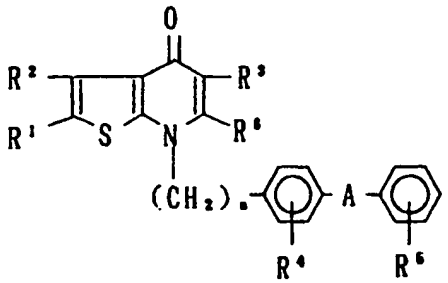
Still another aspect of the present invention relates to a method for treating said circulatory system diseases of hosts, which comprises administering an effective amount of the fused thiophene derivative having the formula I or the pharmaceutical composition thereof to said host.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides fused thiophene derivatives having the formula I and the pharmaceutically acceptable salts thereof, which possess potent angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive diseases, heart diseases, strokes, etc., pharmaceutical compositions comprising an effective amount of the fused thiophene derivative having the formula I and a pharmaceutically acceptable carrier useful in treating said circulatory diseases and processes for preparing such compounds and compositions.

The present invention further provides a method for treating said circulatory system diseases of hosts, which comprises administering an effective amount of the fused thiophene derivative having the formula I or the pharmaceutical composition thereof to said host.

An important group of compounds according to the present invention are the compounds of the formula Ia:

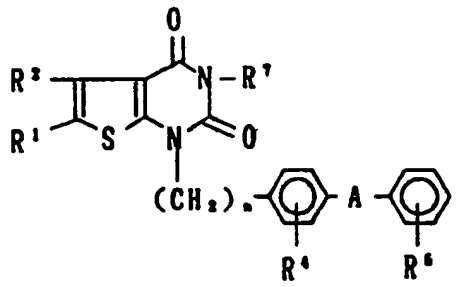


(Ia)

wherein R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^3 is hydrogen, optionally substituted alkyl or alkenyl, or -COD wherein D is hydrogen, alkoxy, hydroxy, halogen, or optionally substituted amino;

R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^6 is hydrogen or optionally substituted alkyl or alkenyl;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2;
and the pharmaceutically acceptable salts thereof.

Another important group of compounds according to the present invention are the compounds of the formula Ib:



(Ib)

wherein R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^7 is a hydrocarbon residue which may be substituted;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and
n is an integer of 1 or 2;
and the pharmaceutically acceptable salts thereof.

With regard to the foregoing formula (I), halogen for R^1 and R^2 include fluorine, chlorine, bromine, and iodine.

The acylamino groups for R^1 and R^2 include a group having the formula: R^8CONH- wherein R^8 is hydrogen or a hydrocarbon residue which may be substituted.

Examples of hydrocarbon residues for R^8 include acyclic hydrocarbon residues such as lower alkyl of 1 to about 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like), lower alkenyl of 2 to about 8 carbon atoms (e.g. vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like), and lower alkynyl of 2 to about 8 carbon atoms (e.g. ethynyl, 2-butynyl, 2-pentynyl, 2-octynyl, and the like); cyclic hydrocarbon residues such as alicyclic hydrocarbon residues of 3 to about 8 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, cyclooctyl and the like), aromatic hydrocarbon residues of about 6 to 12 carbon atoms (e.g. phenyl, naphthyl and the like); etc.

Examples of hydrocarbon residues for R^1, R^2 and R^7 include acyclic hydrocarbon residues such as lower alkyl of 1 to about 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl, octyl, and the like), lower alkenyl of 2 to about 8 carbon atoms (e.g. vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like), and lower alkynyl of 2 to about 8 carbon atoms (e.g. ethynyl, 2-butynyl, 2-pentynyl, 2-octynyl, and the like); cyclic hydrocarbon residues such as alicyclic hydrocarbon residues of 3 to about 8 carbon atoms (e.g. cyclopropyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, cyclooctyl and the like), aromatic hydrocarbon residues of about 6 to 12 carbon atoms (e.g. phenyl, naphthyl and the like); etc.

Said hydrocarbon residues for R^1, R^2 and R^7 may be optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), lower (C_{1-4}) alkyl (e.g. methyl, ethyl, and the like), halogen (e.g. F, Cl, Br and the like), nitro, optionally substituted amino such as amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), N-arylamino (e.g. phenylamino, naphthylamino, etc.), N-aralkylamino (e.g. benzylamino, naphthylmethylamino, etc.) and alicyclic amino (e.g. morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, N-(m-methoxyphenyl)piperazino, etc.), acyloxy such as lower (C_{1-4}) alkanoyloxy (e.g. acetyloxy, etc.) and aroyloxy (e.g. benzoyloxy, etc.), aryl such as phenyl and naphthyl (e.g. phenyl

which may be optionally substituted with halogen, nitro, lower (C_{1-4}) alkoxy, lower (C_{1-4}) alkyl or the like at an optional position on the phenyl ring), or a group having the formula: -COD' wherein D' is hydroxy, lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), or optionally substituted amino such as amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), N-arylamino (e.g. phenylamino, naphthylamino, etc.), N-aralkylamino (e.g. benzylamino, naphthylmethylamino, etc.) and alicyclic amino (e.g. morpholino, piperidino, piperazino, N-phenylpiperazino, etc.). Said hydrocarbon residues for R^1 and R^2 may also be optionally taken together to form a ring.

Alkyl or alkenyl groups for R^3 and R^6 are lower alkyl of 1 to about 8 carbon atoms and lower alkenyl of 2 to about 8 carbon atoms which may be straight or branched. Examples of such alkyl and alkenyl groups for R^3 and R^6 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-octenyl, and the like. Said alkyl or alkenyl groups for R^3 and R^6 may be optionally substituted with hydroxyl, optionally substituted amino such as amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, etc.), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, diethylamino, etc.), halogen, lower (C_{1-4}) alkoxy (e.g. methoxyl, ethoxyl, and the like) and -COD'' wherein D'' is lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like), hydroxy, halogen, or optionally substituted amino as defined above (e.g. amino, N-lower (C_{1-4}) alkyl amino such as methylamino and ethylamino, N,N-dilower (C_{1-4}) alkyl amino such as dimethylamino and diethylamino, N-arylamino such as phenylamino and naphthylamino, N-aralkylamino such as benzylamino and naphthylmethylamino, alicyclic amino such as morpholino, piperidino, piperazino and N-phenylpiperazino, etc).

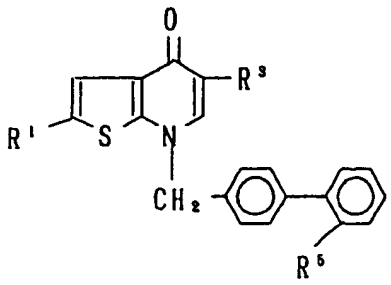
Where R^3 is a group having the formula: -COD, alkoxy groups for D include lower (C_{1-4}) alkoxy (e.g. methoxy, ethoxy, and the like). For D, examples of halogen include Cl, Br and the like, examples of optionally substituted amino include amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, and the like), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, and the like), N-arylamino (e.g. phenylamino, and the like), N-aralkylamino (e.g. benzylamino, naphthylmethylamino, and the like), N-heteroarylamino (e.g. pyridylamino, and the like), N-heteroaralkylamino (e.g. pyridylmethylamino, and the like), alicyclic amino (e.g. morpholino, piperidino, piperazino, piperidylmethyl, N-phenylpiperazino, N-(p-fluorophenyl)piperazino, and the like), wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and the like), hydroxyl, optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkyl amino (e.g. methylamino, ethylamino, and the like), N,N-dilower (C_{1-4}) alkyl amino (e.g. dimethylamino, and the like), alicyclic amino (e.g. morpholino, piperidino, piperazino, N-phenylpiperazino, and the like)), halogen, nitro, lower (C_{1-4}) alkoxy (e.g. methoxyl, ethoxyl), or the like. The compounds wherein D is halogen are useful as synthetic intermediates for the preparation of those wherein D is alkoxy.

R^4 represents hydrogen, halogen (e.g. chlorine, bromine, and the like) or nitro, which may be in the ortho or meta position to the -A- group.

Examples of residues capable of forming an anion and residues convertible into the anion for R^5 include carboxyl, lower (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide ($-NHSO_2CF_3$)-,phosphoric acid, sulfonic acid, and the like. Such residues may include those which are capable of forming anions either chemically or under biological and/or physiological conditions. R^5 is preferable in the ortho position. The compounds wherein R^5 is a residue capable of forming an anion or convertible thereinto chemically (e.g. by oxidation, reduction or hydrolysis) (e.g. cyano and the like), are useful as synthetic intermediates.

A shows that the adjacent phenylene group is bonded to the phenyl group directly or through a spacer whose atomic chain is 2 or less. As the spacer, any one can be exemplified, so long as it is a divalent chain in which the number of atoms constituting the straight chain is 1 or 2, and it may have a side chain. Examples of such spacers include lower (C_{1-4}) alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, $-O-CH_2-$, $-S-CH_2-$, -CH=CH-, etc.

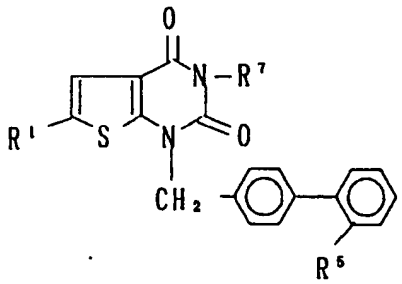
A preferred embodiment of the invention is a compound of the formula (Ia'):



(Ia')

wherein R^1 is lower (C_{1-8}) alkyl; R^3 is hydrogen, optionally substituted lower (C_{1-8}) alkyl (e.g. lower (C_{1-4}) carbalkoxyvinyl, lower (C_{1-4}) alkoxylmethyl, and the like) or COD wherein D is hydrogen, lower (C_{1-4}) alkoxy, hydroxy, or optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkyl amino, phenylamino, methoxybenzylamino, halogenobenzylamino, pyridylmethylamino, piperidylmethylamino, pyridylpiperazinoalkylamino, piperidinoalkylamino, optionally substituted arylpiperazinoalkylamino and the like); and R^5 is carboxyl or tetrazolyl (inter alia tetrazolyl);
and the pharmaceutically acceptable salts thereof.

A further preferred embodiment of the invention is a compound of the formula (Ib'):

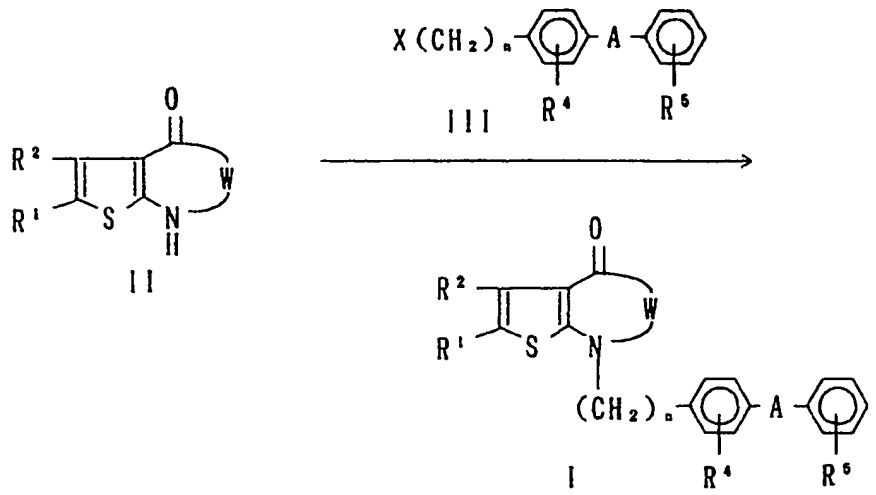


(Ib')

wherein R^1 is lower (C_{1-8}) alkyl; R^7 is hydrogen, lower (C_{1-8}) alkyl which may be optionally substituted with optionally substituted aryl, optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkyl amino, N,N-dilower (C_{1-4}) alkyl amino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, and the like) or COD wherein D is lower (C_{1-4}) alkoxy, hydroxy, or optionally substituted amino (e.g. amino, N-lower (C_{1-4}) alkyl amino, N,N-dilower (C_{1-4}) alkyl amino, phenylamino, benzylamino, and the like), (C_{3-8}) cycloalkyl or optionally substituted aryl (e.g. halogenophenyl);
and R^5 is carboxyl or tetrazolyl (inter alia tetrazolyl);
and the pharmaceutically acceptable salts thereof.

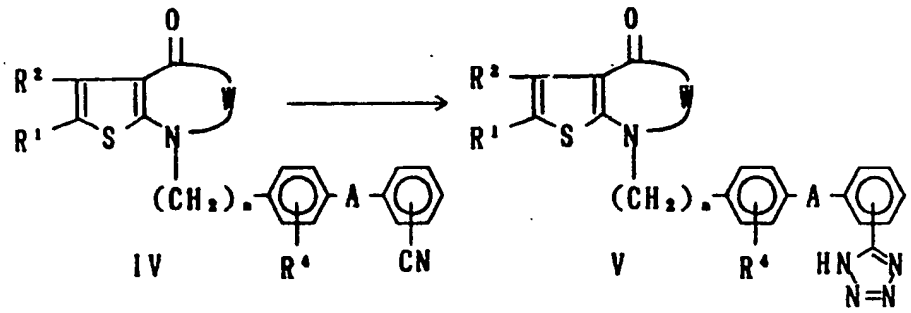
The compounds (I) of the present invention may be prepared by several reaction schemes, as illustrated below for a preferred compound.

Scheme A



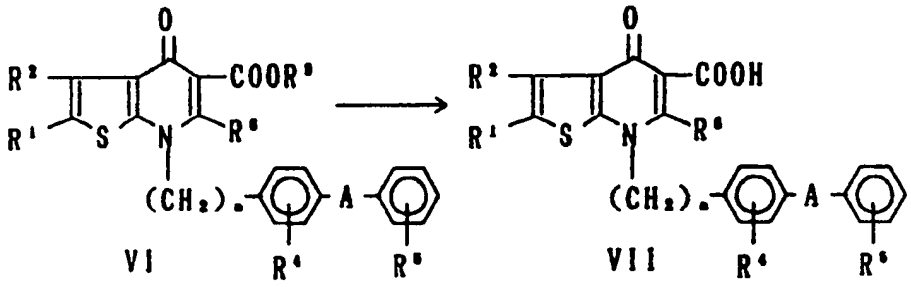
wherein R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, and X is halogen.

Scheme B



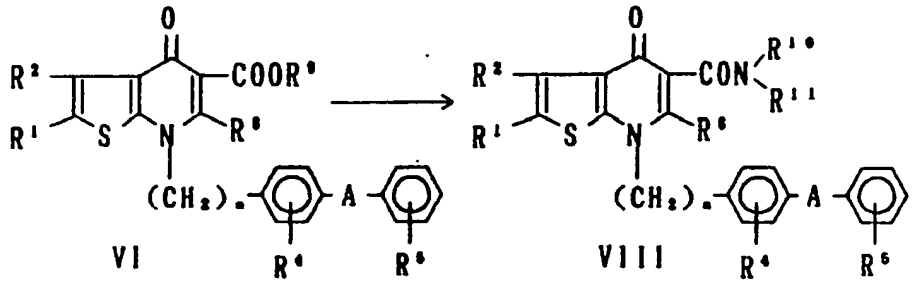
wherein each group is of the same meaning as defined above.

Scheme C



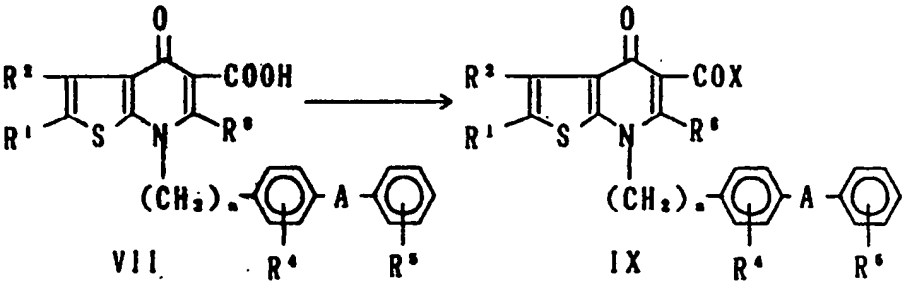
wherein R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and R^9 is lower (C_{1-4}) alkyl.

Scheme D



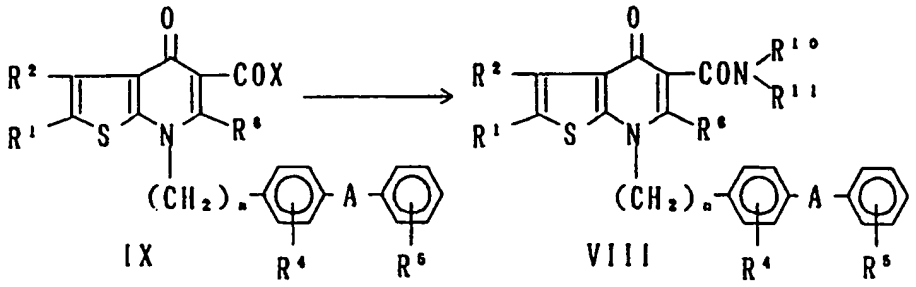
wherein R^1, R^2, R^4, R^5, R^6, R^9, A and n have the above-defined meanings, and R^{10} and R^{11} are each independently hydrogen or a hydrocarbon residue.

Scheme E



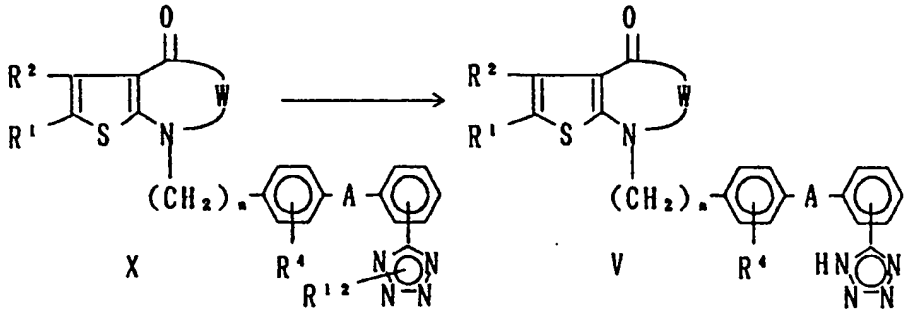
wherein R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and X is halogen.

Scheme F



wherein R^1, R^2, R^4, R^5, R^6, R^{10}, R^{11}, X, A and n have the above-defined meanings.

Scheme G



wherein R^1, R^2, R^4, A, W and n have the above-defined meanings and R^{12} is a protective group.

The reaction as illustrated in Scheme A is an alkylation using an alkylating agent in the presence of a base. One molar portion of the compound (II) is employed with 1 to 3 moles of the base and about 1 to about 3 moles of the alkylating agent. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, dimethylsulfoxide, acetonitrile, acetone, ethylmethylketone, and the like. Examples of such bases include sodium hydride, potassium t-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, and the like. Examples of such alkylating agents include substituted halides (e.g. chlorides, bromides, iodides, and the like), substituted sulfonate esters (e.g. methyl p-toluenesulfonate esters, and the like), etc.

The reaction conditions may vary depending on the combination of the base and the alkylating agent. A temperature in the range of from ice-cooling to 100 °C is preferred and a reaction period of from about 1 to about 10 hours is preferably employed.

The cyano substituent on the benzene of the compounds (IV) is reacted with various azides to form the tetrazole compounds (V) as illustrated in Scheme B. One molar portion of the compound (IV) is employed with about 1 to about 10 moles of the azide. The reaction is conventionally conducted in solvents such as dimethylformamide, dimethylacetamide, toluene, benzene, and the like.

Examples of such azides include trialkyl-tin azide, triphenyl-tin azide, hydrogen azide, and the like. In the case where the organo-tin azide compound is employed, the reaction is carried out in toluene or benzene by heating under reflux for a period of from about 10 to about 30 hours. When the hydrogen azide is used, 5 moles of sodium azide and ammonium chloride per compound (IV) are employed and the reaction is conducted in dimethylformamide at a temperature ranging from about 100 °C to about 130 °C for 1 to 10 days. During this reaction, it is preferable to facilitate working by adding an appropriate amount of

sodium azide and ammonium chloride.

The reaction as illustrated in Scheme C is hydrolysis of the ester (VI) into the carboxylic acid (VII) in the presence of an alkali. One molar portion of the compound (VI) is employed with 1 to 3 moles of the alkali. The reaction is conventionally conducted in solvents such as alcohols containing water (e.g. methanol, ethanol, methylcellosolve, and the like). Examples of such alkalis include sodium hydroxide, potassium hydroxide, and the like. The reaction is preferably conducted at a temperature in the range from room temperature to 100° C for a period from about 1 to about 10 hours.

The compounds (VI) are reacted with various amines to form the amide compounds (VIII) as illustrated in Scheme D. One molar portion of the compound (VI) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) or without a solvent. The reaction is preferably conducted at a temperature in the range from room temperature to 200° C. Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, phenetylamine, N-benzyl-N-methylamine, o-methoxybenzylamine, etc.), arylamines (e.g. aniline, N-methylaniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, 3-(p-fluorophenylpiperazino)propylamine, etc.), and the like.

The compounds (VII) are treated with various halogenating agents to form the acid halides (IX) as illustrated in Scheme E. One molar portion of the compound (VII) is employed with about 1 to 5 moles of the halogenating agent. The reaction is conventionally conducted in solvents such as halogenated hydrocarbons (e.g. $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, and the like), ethers (e.g. tetrahydrofuran, dioxane, and the like) and aromatic hydrocarbons (e.g. benzene, toluene, and the like). Examples of such halogenating agents include oxalyl chloride, thionyl chloride, phosphorous oxychloride, phosphorous trichloride, phosphorous pentachloride, etc. The reaction is preferably conducted at a temperature in the range from room temperature to 100° C for a period from about 1 to about 10 hours.

The acid halides (IX) are reacted with various amines to form the amide compounds (VIII) as illustrated in Scheme F. One molar portion of the compound (IX) is employed with about 2 to 50 moles of the amine. The reaction is conventionally conducted in solvents such as alcohols (e.g. methanol, ethanol, and the like) and ethers (e.g. ethyl ether, tetrahydrofuran, dioxane, and the like). Examples of such amines include ammonia, alkylamines (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, butylamine, hydroxyethylamine, etc.), aralkylamines (e.g. benzylamine, phenetylamine, N-benzyl-N-methylamine, o-methoxybenzylamine, etc.), arylamines (e.g. aniline, N-methylaniline, etc.), heteroaralkylamines (e.g. 2-, 3- or 4-pyridylmethylamine, etc.), alicyclic amines (e.g. morpholine, piperidine, piperazine, N-phenylpiperazine, 2-piperidylmethylamine, 3-(p-fluorophenylpiperazino)propylamine, etc.), and the like.

The protective group (R^{12}) on the tetrazole compound (X) leaves to form the tetrazole compound (V) as illustrated in Scheme G. Reaction conditions may vary depending on the protective group (R^{12}) used. When R^{12} is triphenylmethyl (trityl), 2-tetrahydropyranyl, methoxymethyl, ethoxymethyl, or the like, the leaving of the protective group is conveniently conducted in aqueous alcohols (e.g. methanol, ethanol, etc) containing from about 0.5N to about 2N hydrochloric acid or acetic acid, or in a mixture of trifluoroacetic acid and water (1:2 ~5) at room temperature for a period from about 1 to about 10 hours.

The compounds (I) thus produced via the reaction processes as depicted in Schemes A, B, C, D, E, F and G can be isolated and purified from the reaction mixture according to conventional methods such as, for example, evaporation of solvents, extraction by water or organic solvents, concentration, neutralization, recrystallization, distillation, column chromatography and the like, to obtain a crystalline or oily product.

The compounds (I) of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include but are not limited to the following: salts with inorganic acids such as hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

The starting materials (II) can be easily prepared by or according to the known techniques, for example, as disclosed in:

(1) P. Blaszkiewicz, H. Vorbruggen and H. J. Kesler (Schering AG): DOS 2, 447,477 (15. 4. 76); Chem. Abst., 85, 46627 (1976),

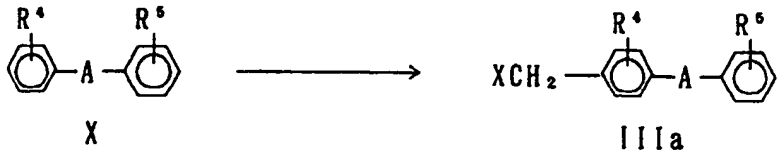
(2) Y. Kuwada, K. Meguro, Y. Sato and T. Fugono (Takeda Chem.): DOS 2, 435,025 (6. 25. 75); Chem. Abst., 82, 156252 (1975), etc.

Among the starting materials (III), the compounds wherein n is 1 (the compounds (IIIa)) is prepared by

the known techniques as disclosed in Japanese Patent Laid Open No. 23868/1988; and No. 117876/1989, and European Patent Laid Open No. 0323841.

As illustrated in Scheme H, the compounds (IIIa) can also be easily prepared by halogenomethylation of the compounds (X) commercially available or easily prepared according to methods described in known literatures such as, for example, A. A. Vansheidt et al., Khim. Nauka i Prom., 2, 799 (1957).

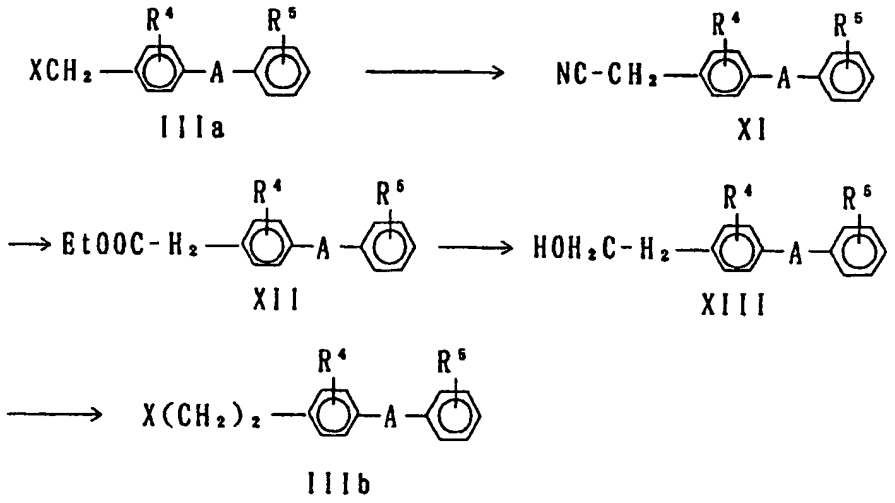
Scheme H



wherein each group has the above-defined meaning.

The compound (III) wherein n is 2 (the compounds (IIIb)) can be prepared from the compounds (IIIa) according to the methods as illustrated in Scheme I.

Scheme I



wherein each group has the above-defined meaning.

The compounds (I) and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, rabbits, rats, etc.). Further, the compounds (I) and salts thereof according to the present invention are of quite low toxicity and useful in treating not only hypertension but also circulatory system diseases such as heart diseases, strokes and the like.

For therapeutic use, the compounds (I) and salts thereof can be administered as pharmaceutical compositions (e.g, powders, granules, tablets, pills, capsules, injections, solutions and the like) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time

of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. When used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, selected from the range of about 10 mg to 100 mg a day orally and from the range of about 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention.

Example

The invention is further illustrated but in no way limited by the following reference examples, working examples, pharmaceutical examples and experimental examples.

In the specification of the present application, examples of the abbreviations used are given below. Me: Methyl, Et: Ethyl, Pr: Propyl, Bu: Butyl, iBu: Isobutyl, tBu: Tert-butyl, Ph: Phenyl, DMF: Dimethylformamide.

Reference Example 1

Isobutyl 2-ethyl-4-hydroxythieno[2,3-b]-pyridine-5-carboxylate

To 10 ml of isobutyl alcohol were added 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylic acid (200 mg, 0.9 mmol) and boron trifluoride-ethyl ether (47 %, 0.5 ml) and the mixture was heated under reflux for 5 hours. The reaction mixture was allowed to cool and concentrated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/ethyl acetate (3:1) to give 80 mg (31 %) of the title compound as colorless crystals.

M.p. 156-158 °C.

IR (KBr)cm^{-1}: 1700, 1595, 1520.

NMR ($CDCl_3$) δ : 1.05(6H, d, J=6.6Hz), 1.40(3H, t, J=7.4Hz), 2.0-2.2(1H, m), 2.94(2H, q, J=7.4, 15.0Hz), 4.20(2H, d, J=6.6Hz), 7.16(1H, s), 8.84(1H, s).

Elemental Analysis for $C_{14}H_{17}NO_3 \cdot H_2O$

	C (%)	H (%)	N (%)
Calcd:	C, 63.38;	H, 5.70;	N, 15.84
Found:	C, 63.70;	H, 5.44;	N, 15.50.

Reference Example 2

2-Methoxyethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate

To 5 ml of benzene were added 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylic acid (380 mg, 1.7 mmol) and DMF (0.13 ml, 1.7 mmol) and the mixture was heated to 60 °C. To the reaction mixture was added thionyl chloride (0.15 ml, 2.1 mmol) and the mixture was stirred at 60 °C for 3 hours and allowed to cool on an ice bath. The precipitated product was collected by filtration and washed with benzene. The resulting precipitate (223 mg) was dissolved in a mixture of 2-methoxyethanol (0.3 ml) and CH_2Cl_2 (5 ml) and triethyamine (0.7 ml) were added to the solution. The mixture was stirred for 30 minutes and poured into chloroform. The resulting mixture was washed with 1N hydrochloric acid, dried ($MgSO_4$) and evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/hexanes/chloroform (1:1:1) and then chloroform/methanol (9:1) to give 200 mg (41 %) of the title compound as colorless powders.

IR (KBr)cm^{-1}: 1700, 1590, 1530, 1480.

NMR ($CDCl_3$) δ : 1.39(3H, t, J=7.4Hz), 2.94(2H, q, J=7.4, 15.0Hz), 3.45(3H, s), 3.7-3.8(2H, m), 4.5-4.6(2H, m), 7.17(1H, s), 8.87(1H, s).

Elemental Analysis for $C_{13}H_{15}NO_4S$

	C (%)	H (%)	N (%)
Calcd:	C, 55.50;	H, 5.37;	N, 4.98
Found:	C, 55.47;	H, 5.38;	N, 4.95

Reference Example 3

Ethyl 2-ethyl-4-hydroxy-3-nitrothieno[2,3-b]pyridine-5-carboxylate

A solution of ethyl 2-ethyl-4-hydroxythieno-[2,3-b]pyridine-5-carboxylate (1.0 g, 4.0 mmol) in conc. sulfuric acid (10 ml) was cooled to -5 °C and a solution of sodium nitrate (370 mg, 4.3 mmol) in conc. sulfuric acid (5 ml) was added dropwise to the chilled solution. The reaction mixture was stirred at -3 °C to -5 °C for 1 hour, and poured into ice-water. The precipitated product was collected by filtration and washed with cold water and then ethanol. The resulting precipitate was dissolved in chloroform, washed with a saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated in vacuo. The resulting yellow solid was washed with a mixture of ether/hexanes, and dried to give 960 mg (81 %) of the title compound. M.p. 194-201 °C (dec.).

IR (KBr)cm^{-1}: 1700, 1600, 1590, 1530.

NMR ($CDCl_3$) δ : 1.42(3H, t, J=7.4Hz), 1.47(3H, t, J=7.2Hz), 3.05(2H, q, J=7.4, 15.0Hz), 4.50(2H, q, J=7.2, 14.4Hz), 8.93(1H, s).

Elemental Analysis for $C_{12}H_{12}N_2O_5S$

	C (%)	H (%)	N (%)
Calcd:	C, 48.64;	H, 4.08;	N, 9.45
Found:	C, 48.48;	H, 4.01;	N, 9.28

Reference Example 4

Ethyl 2-ethyl-7-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate

To a solution of ethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (1.00 g, 4 mmol) in 20 ml of DMF) was added sodium hydride (60 % dispersion in oil, 160 mg) and the mixture was stirred for 10 minutes. To the reaction mixture was added 4-[2'-(N-trityltetrazol-5-yl)phenyl]benzyl bromide (2.23 g, 4 mmol) and the mixture was heated at 90 °C for 1 hour with stirring. The reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/dichloromethane (1:1) to give 2.24 g (77 %) of the title compound as white crystals. M.p. 195-198 °C.

IR (KBr)cm^{-1}: 1730, 1705, 1620.

NMR ($CDCl_3$) δ : 1.27(3H, t, J=9.6Hz), 1.39(3H, t, J=6.8Hz), 2.72(2H, q, J=8.9, 15.0Hz), 4.38(2H, q, J=7.2, 13.8Hz), 5.02(2H, s), 6.80-8.0(9H, m), 8.29(1H, s).

Elemental Analysis for $C_{15}H_{17}N_5O_3S$

	C (%)	H (%)	N (%)
Calcd:	74.26	5.12	9.62
Found:	74.09	5.18	9.50

The following compounds (II) can be easily prepared by or according to the known techniques, for example, as disclosed in:

(1) P. Blaszkiewicz, H. Vorbruggen and H. J. Kesler (Schering AG): DOS 2, 447,477 (15. 4. 76); Chem. Abst., 85, 46627 (1976),

(2) Y. Kuwada, K. Meguro, Y. Sato and T. Fugono (Takeda Chem.): DOS 2, 435,025 (6. 25. 75); Chem. Abst., 82, 156252 (1975),

(3) R. K. Russell, J. B. Plress, R. A. Rampulla, J. J. McNally, R. Falotico, J. A. Keiser, D. A. Bright and A. Tobia, J. Med. Chem., 31, 1786 (1988),

(4) M. Suwada, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi and H. Fuumi, Chem. Pharm. Bull., 37, 2091 (1989),

(5) M. Sugiyama, T. Sakamoto, K. Tabata and H. Fuumi, Chem. Pharm. Bull., 37, 2717 (1989),

(6) G. D. Madding and M. D. Thompson, J. Heterocyclic Chem., 24, 581 (1987),

(7) J. Barker, P. R. Huddleston and D. Holmes, J. Chem. Research (S), 1985, 214,

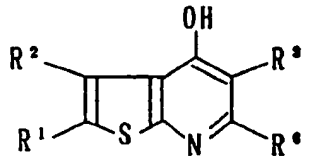
(8) J. Barker, P. R. Huddleston and D. Holmes, J. Chem. Research (S), 1986, 122,

(9) M. A. Khan and A. E. Guarconi, J. Heterocyclic Chem., 14, 807 (1977),

(10) K. Ogawa, I. Yamawaki, Y. Matsusita, N. Nomura and I. Okazaki, WO 89/02432.

The compounds (III) can alternatively be prepared in the same manner as described in Reference Example 1, 2, or 3.

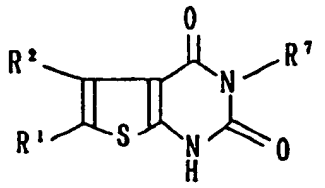
TABLE 1



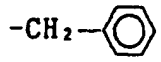
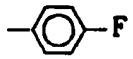
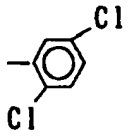
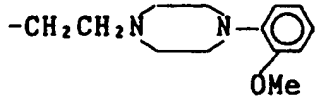
(II)

Reference Example No.	R^1	R^2	R^3	R^6	MP.(°C)
5-1	Br	H	COOEt	H	208-209
5-2	H	H	COOEt	H	105-108
6	Me	H	COOEt	H	122-124
7	Pr	H	COOEt	H	74- 75
8	Et	H	$COOCH_2CH_2OMe$	H	powder
9	Et	H	CH_2OH	H	> 260 (decomp.)

TABLE 2

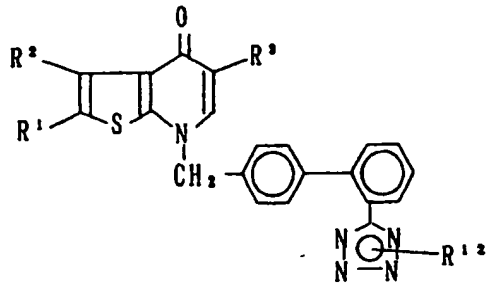


(II)

Reference Example No.	R^1	R^2	R^7	MP (°C)
10	Et	H	Bu	217-220
11	Et	H		259-262
12	Et	H	Et	243-244
13	Et	H		>290
14	Et	H		268-275
15	Et	H		285-288
16	Et	H	$-CH_2COOEt$	201-204
17	Et	H		239-241

The following compounds (Reference Examples 18-32) were prepared in the same manner as in Reference Example 4.

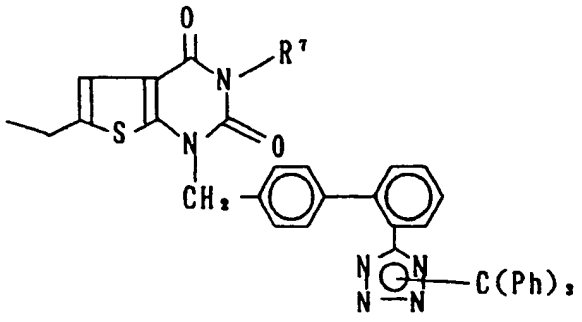
TABLE 3



Reference Example No.	R^1	R^2	R^3	R^{12}	Yield (%)	MP (°C)
18	Et	H	$-COOCH_2CH_2OCH_3$	$-C(Ph)_3$	30	192-198
19	Et	H	-COOiBu	$-C(Ph)_3$	40	209-212
20	Et	NO_2	-COOEt	$-C(Ph)_3$	34	
21	Me	H	-COOEt	$-C(Ph)_3$	53	205-207
22	Pr	H	-COOEt	$-C(Ph)_3$	51	181-187
23	Br	H	-COOEt	$-C(Ph)_3$	47	129-133
24	H	H	-COOEt	$-C(Ph)_3$	50	137-139
25	Et	H	$-CH_2OH$	$-C(Ph)_3$	46	powder
26	Et	H	H	$-C(Ph)_3$	46	
27	Et	H	-CHO	$-C(Ph)_3$	67	150-156
28	Et	H	-CH=CH-COOtBu	$-C(Ph)_3$	56	powder
29	Et	H	-COOEt	-COOtBu	62	
30	CN	H	-COOEt	$-C(Ph)_3$	21	129-131
31	Et	H	$-CONCH_2Ph$ CH_3	$-C(Ph)_3$	56	169-171
32	Et	H	$-CH_2OMe$	$-C(Ph)_3$	26	powder

The following compounds (Reference Examples 33-40) were prepared in the same manner as in Reference Example 4.

TABLE 4a



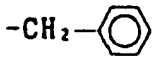
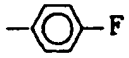
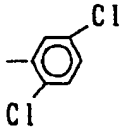
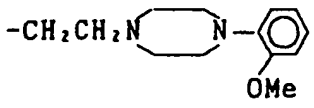
Reference Example No.	R^7	MP (°C)	Yield (%)
33	Bu	173-176	57
34		204-207	47
35	Et	117-122	57
36		192-193	67
37		193-197	79
38		141-144	48
39	$-CH_2COOEt$	181-183	63
40		powder	93

TABLE 4b

Reference Example No.	^{1}H-NMR (200MHz , $CDCl_3$) δ
33	0.96(3H, t), 1.24(3H, t), 1.3-1.5(2H, m), 1.5-1.7(2H, m), 2.66(2H, q), 4.04(2H, t), 5.01(2H, s), 7.00(1H, s), 6.8-7.5(22H, m), 7.9-8.0(1H, m)
34	1.22(3H, t), 2.65(2H, q), 5.00(2H, s), 5.23(2H, s), 7.00(1H, s), 6.8-8.0(28H, m)
35	1.24(3H, t), 1.27(3H, t), 2.66(2H, q), 4.11(2H, q), 5.01(2H, s), 6.8-7.5(23H, m), 7.9-8.0(1H, m),
36	1.28(3H, t), 2.72(2H, q), 5.03(2H, s), 6.8-8.0(28H, m)
37	1.26(3H, t), 2.68(2H, q), 5.06(2H, q), 6.8-8.0(27H, m)
38	1.23(3H, t), 1.2-2.6(10H, m), 2.65(2H, q), 4.8-5.0(1H, m), 4.97(2H, s), 6.8-7.9(24H, m)
39	1.23(3H, t), 1.29(3H, t), 2.65(2H, q), 4.24(2H, q), 4.79(2H, s), 5.02(2H, s), 6.8-8.0(24H, m)
40	1.23(3H, t), 2.64(2H, q), 2.7-3.2(10H, m), 3.85(3H, s), 4.2-4.4(2H, m), 5.03(2H, s), 6.8-7.5(27H, m), 7.9-8.0(1H, m)

Working Example 1

A: Ethyl 2-ethyl-7-[2'-cyanobiphenyl-4-yl)methyl]-4-oxo-thieno[2,3-b]pyridine-5-carboxylate

Ethyl 2-ethyl-4-hydroxythieno[2,3-b]-pyridine-5-carboxylate (250 mg, 1 mmol) and 4-(2'-cyanophenyl)-benzyl chloride (250 mg, 1.1 mmol) were dissolved in 5 ml of N,N-dimethylformamide (DMF). To the solution was added potassium carbonate (150 mg) and the mixture was stirred at 90 °C for 2 hours. The reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with ethyl acetate/dichloromethane (1:1) to give 254 mg (60 %) of the title compound as crystals.

NMR ($CDCl_3$) δ : 1.30(3H, t, J=6Hz), 1.39(3H, t, J=6Hz), 2.81(2H, q, J=6, 15Hz), 4.40(2H, q, J=6, 13.5Hz), 5.27(2H, s), 7.25-8.0(9H, m), 8.37(1H, s).

B: Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate and 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylic acid

A solution of the compound (250 mg, 0.59 mmol) prepared in Working Example 1A, sodium azide (390 mg, 5.9 mmol) and ammonium chloride (300 mg, 5.9 mmol) in DMF (15 ml) was stirred at 110 °C for 10 days. After cooling, the reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue

was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (9:1) to give 37 mg (13 %) of ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate as pale yellow powders.

IR (KBr)cm^{-1}: 1720, 1600, 1550, 1505.

NMR (CD_3OD) δ : 1.31(3H, t, J=7.6Hz), 1.36(3H, t, J=7.0Hz), 2.85(2H, q, J=7.6, 15.0Hz), 4.33(2H, q, J=7.0, 14.2Hz), 5.45(2H, s), 7.15(2H, d, J=8.6Hz), 7.21(1H, s), 7.28(2H, d, J=8.6Hz), 7.5-7.7(4H, m), 8.75(1H, s).

The column was further eluted with chloroform/methanol (9:1) to give 7 mg (2.7 %) of 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylic acid as white solids.

IR (KBr)cm^{-1}: 1650, 1605, 1580, 1540, 1505.

NMR (CD_3OD) δ : 1.34(3H, t, J=7.6Hz), 2.89(2H, q, J=8.6, 15.0Hz), 5.47(2H, s), 7.15(2H, d, J=8.2Hz), 7.24(1H, s), 7.28(2H, d, J=8.2Hz), 7.5-7.7(4H, m).

Working Example 2

Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate

A solution of the compound (727 mg, 1 mmol) prepared in Reference Example 4 in 20 ml of trifluoroacetic acid/water (1:3) was stirred at room temperature for 1 hour. The reaction mixture was poured into water followed by extraction with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (9:1) to give 1.28 g (86 %) of the title compound as colorless crystals. This product was identified by comparing with NMR and IR spectra of the compound obtained in Working Example 1B.

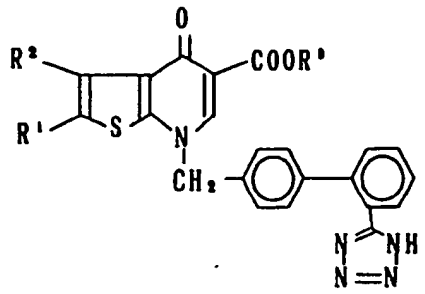
M.p. 161-164 °C.

Elemental Analysis for $C_{26}H_{23}N_5O_3S \cdot H_2O$

	C (%)	H (%)	N (%)
Calcd:	C, 62.01;	H, 5.00;	N, 13.91
Found:	C, 62.05;	H, 4.59;	N, 13.78

The following compounds as listed in Table 5 were prepared in the same manner as in Working Examples 2.

TABLE 5a



Working Example No.	R^1	R^2	R^9	MP.(°C)	IR(KBr) (cm^{-1})
3	Br	H	Et	254-260 (decomp.)	1725, 1680, 1610, 1560, 1500
4	H	H	Et	245-249	1720, 1600, 1560
5	Me	H	Et	249-253	1710, 1675, 1605, 1560, 1505
6	n-Pr	H	Et	108-110	1720, 1605, 1550, 1505
7	Et	H	i-Bu	256-259 (decomp.)	1720, 1670, 1605, 1560, 1500
8	Et	H	CH_2CH_2OMe	201-210	1720, 1680, 1605, 1560, 1505
9	Et	NO_2	Et	214 ~ (decomp.)	1720, 1700, 1615, 1550, 1510

TABLE 5b

Working Example No.	NMR (d_6-DMSO) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
3	1.29(3H,t,J=7.2Hz),4.24(2H,q, J=7.2,14.2Hz),5.46(2H,s),7.13(2H, d,J=8.2Hz),7.29(2H,d,J=8.2Hz), 7.5-7.7(5H,m),8.79(1H,s)	$C_{24}H_{18}BrN_5O_3S$ 53.74;3.38;13.06 53.57;3.34;12.80
4	1.29(3H,t,J=7.2Hz),4.24(2H,q, J=7.2,14.2Hz),5.51(2H,s),7.13(2H, d,J=8.0Hz),7.27(2H,d,J=8.0Hz), 7.3-7.8(8H,m),8.80(1H,s)	$C_{24}H_{19}N_5O_3S \cdot 0.5H_2O$ 61.79;4.32;15.01 61.94;4.17;14.80
5	1.29(3H,t,J=7.2Hz),2.44(3H,d, J=1.0Hz),4.23(2H,q,J=7.2,14.2Hz), 5.45(2H,s),7.08(1H,d,J=1.0Hz), 7.13(2H,d,J=8.0Hz),7.25(2H,d, J=8.0Hz),7.5-7.7(4H,m),8.74(1H,s)	$C_{25}H_{21}N_5O_3S$ 63.68;4.49;14.85 63.39;4.47;14.67
6	0.91(3H,t,J=7.2Hz),1.28(3H,t, J=7.0Hz),1.61(2H,q,J=7.2,15.0Hz), 2.76(2H,t,J=7.6Hz),4.23(2H,q, J=7.0,14.2Hz),5.45(2H,s),7.10(1H, s),7.12(2H,d,J=8.4Hz),7.26(2H,d, J=8.4Hz),7.5-7.7(4H,m), 8.74(1H,s)	$C_{27}H_{25}N_5O_3S \cdot H_2O$ 62.65;5.26;13.53 62.55;4.84;13.38
7	0.96(6H,d,J=6.8Hz),1.23(3H,t, J=7.4Hz),1.9-2.1(1H,m),2.80(2H, q,J=7.4,15.0Hz),3.97(2H,d, J=6.6Hz),5.46(2H,s),7.11(1H, s),7.13(2H,d,J=8.0Hz),7.27(2H,d, J=8.0Hz),7.5-7.7(4H,m), 8.70(1H,s)	$C_{28}H_{27}N_5O_3S \cdot 0.5H_2O$ 64.35;5.40;13.40 64.22;5.24;13.47
8	1.23(3H,t,J=7.4Hz),2.81(2H,q, J=7.4,15.0Hz),3.30(3H,s),3.62 2H,t,J=4.8Hz),4.31(2H,t,J=4.8Hz) 5.46(2H,s),7.11(1H,s),7.12(2H,d, J=8.0Hz),7.25(2H,d,J=8.0Hz), 7.5-7.7(4H,m),8.73(1H,s)	

TABLE 5b

Working Example No.	NMR (d_6-DMSO) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
9	1.20(3H,t,J=7.4Hz),1.29(3H,t, J=7.0Hz),2.83(2H,q,J=7.4,15.4Hz), 4.24(2H,q,J=7.0,14.0Hz),5.53(2H, s),7.14(2H,d,J=8.2Hz),7.30(2H,d, J=8.2Hz),7.5-7.7(4H,m),8.86(1H,s)	$C_{28}H_{22}N_6O_5S \cdot H_2O$ 56.93;4.41;15.32 57.12;4.05;15.26

Working Example 10

2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylic acid

Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate (600 mg, 1.235 mmol) was dissolved in 6 ml of 1N sodium hydroxide and the mixture was heated at 100 °C for 20 minutes with stirring. After cooling, 7 ml of 1N hydrochloric acid was added to the reaction mixture and the mixture was extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting crystal was washed with dichloromethane and dried to give 550 mg of the title compound as white crystals. This product was identified by comparing with NMR and IR spectra of the compound obtained in Working Example 1B. M.p. 153-157 °C.

Elemental Analysis for $C_{24}H_{19}N_5O_3S \cdot 3.5H_2O$

	C (%)	H (%)	N (%)
Calcd:	C, 55.38;	H, 5.03;	N, 13.48
Found:	C, 54.75;	H, 3.93;	N, 13.15

Working Example 11

A: Ethyl 2-ethyl-7-[(2'-t-butoxycarbonylbiphenyl-4-yl)methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate

To 10 ml of DMF were added ethyl 2-ethyl-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (200 mg, 0.8 mmol), 4-(2-t-butoxycarbonylphenyl)benzyl bromide (300 mg, 0.9 mmol) and cesium carbonate (650 mg, 2.0 mmol) and the mixture was stirred at 60 °C for 3 hours and further at 100 °C for an additional hour. After cooling, the reaction mixture was poured into water followed by extraction with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel to give 258 mg (62 %) of the title compound as crystals.

IR (KBr)cm^{-1}: 1720, 1705, 1690, 1510.

NMR ($CDCl_3$) δ : 1.20(9H, s), 1.32(3H, t, J=7.6Hz), 1.41(3H, t, J=7.2Hz), 2.81(2H, q, J=7.6, 14.6Hz), 4.40(2H, q, J=7.2, 14.2Hz), 5.23(2H, s), 7.2-7.5(8H, m), 7.81(1H, dd, J=1.6, 7.6Hz), 8.42(1H, s).

Elemental Analysis for $C_{30}H_{31}NO_5S$

	C (%)	H (%)	N (%)
Calcd:	C, 69.61;	H, 6.04;	N, 2.71
Found:	C, 69.85;	H, 6.15;	N, 2.37

B: Ethyl 2-ethyl-7-[(2'-carboxybiphenyl-4-yl)methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate

To 5 ml of trifluoroacetic acid under ice-cooling were added the compound (200 mg, 0.39 mmol) prepared in Working Example 11A and anisole (0.1 ml) and the mixture was stirred for 2.5 hours. The reaction mixture was concentrated to dryness in vacuo. To the resulting residue was added dichloromethane followed by evaporation to dryness in vacuo. These treatments were additionally repeated twice and ether was added to the resulting residue to precipitate solids which were filtered and dried to give 167 mg (93 %) of the title compound as pale yellow powders.

IR (KBr)cm^{-1}: 1715, 1680, 1605.

NMR (d_6-DMSO) δ : 1.23(3H, t, J=7.4Hz), 1.29(3H, t, J=7.2Hz), 2.80(2H, q, J=7.4, 15.0Hz), 4.23(2H, q, J=7.2, 13.8Hz), 5.49(2H, s), 7.11(1H, s), 7.3-7.6(7H, m), 7.73(1H, d, J=7.4Hz), 8.77(1H, s).

Elemental Analysis for $C_{26}H_{23}NO_5S \cdot 0.3H_2O$

	C (%)	H (%)	N (%)
Calcd:	C, 66.88;	H, 5.09;	N, 3.00
Found:	C, 67.03;	H, 5.14;	N, 2.95

Working Example 12

2-Ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine

A mixture of the compound (123 mg, 0.25 mmol) prepared in Working Example 2 and benzylamine (2 ml) was stirred at 60 °C for 3 days. After cooling, the reaction mixture was poured into chloroform, washed twice with 1N hydrochloric acid, dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (19:1 to 9:1) to give 63 mg (45 %) of the title compound as crystals. M.p. 177-180 °C.

IR (KBr)cm^{-1}: 1650, 1590, 1550, 1500.

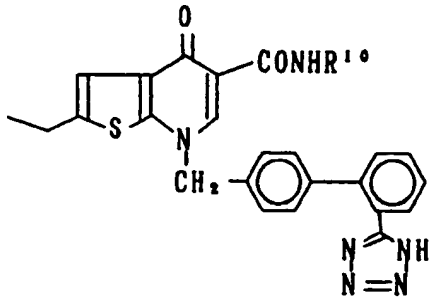
NMR (d_6-DMSO) δ : 1.25(3H, t, J=7.4Hz), 2.83(2H, q, J=7.4Hz, 14.2Hz), 4.56(2H, d, J=5.8Hz), 5.57-(2H, s), 7.0-7.7(14H, m), 8.95(1H, s).

Elemental Analysis for $C_{31}H_{26}N_6O_2S$

	C (%)	H (%)	N (%)
Calcd:	C, 68.11;	H, 4.79;	N, 15.37
Found:	C, 68.06;	H, 4.79;	N, 15.17

The following compounds as listed in Table 6 were prepared in the same manner as in Working Examples 12.

TABLE 6a



Working Example No.	R¹⁰	MP.(°C)	IR(KBr) (cm⁻¹)
13	H	267-270	1635, 1575, 1540, 1500
14	$CH_2CH(Me)_2$	248-251 (decomp.)	1655, 1590, 1555, 1525, 1510
15	CH_2CH_2OH	155-159	1655, 1595, 1550, 1520
16	C_6H_5	215-218	1655, 1595, 1545, 1505

TABLE 6b

Working Example No.	NMR (d_6-DMSO) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
13	1.25(3H,t,J=7.6Hz),2.83(2H,q, J=7.6,14.8Hz),5.54(2H,s),7.12(2H, d,J=8.2Hz),7.22(1H,s),7.26(2H,d, J=8.2Hz),7.5-7.7(4H,m),8.91(1H,s), 9.46(1H,bs)	$C_{24}H_{20}N_6O_2S \cdot H_2O$ 60.75;4.67;17.71 61.09;4.41;17.37
14	0.93(6H,d,J=6.6Hz),1.25(3H,t, J=7.4Hz),1.7-1.9(1H,m),2.84(2H,d, J=7.4,14.0Hz),3.18(2H,t,J=6.2Hz), 5.55(2H,s),7.11(2H,d,J=8.2Hz), 7.19(1H,s),7.25(2H,d,J=8.2Hz), 7.5-7.7(4H,m),8.90(1H,s)	$C_{28}H_{28}N_6O_2S \cdot H_2O$ 63.38;5.70;15.84 63.70;5.44;15.50
15	1.25(3H,t,J=7.4Hz),2.84(2H,q, J=7.4,16.0Hz),3.3-3.6(4H,m), 4.81(1H,bs),5.55(2H,s),7.11(2H, d,J=8.2Hz),7.18(1H,s),7.24(2H,d J=8.2Hz),7.5-7.7(4H,m),8.31(1H,s), 8.90(1H,s)	
16	1.27(3H,t,J=7.4Hz),2.87(2H,q, J=7.4,14.6Hz),5.59(2H,s),7.0-7.8 (14H,m),9.05(1H,s)	$C_{30}H_{24}N_6O_2S \cdot 0.5H_2O$ 66.53;4.65;15.52 66.28;4.51;15.26

Working Example 17

Ethyl 3-acetylamino-2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate

Ethyl 2-ethyl-3-nitro-7-[[2'-(N-trityltetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylate (200 mg, 0.26 mmol) was dissolved in a mixture of acetic anhydride (6 ml), acetic acid (6 ml), dioxane (4 ml) and tetrahydrofuran (5 ml) and the solution was heated to 70 °C. To the heated solution were added zinc powders (85 mg) and the reaction mixture was stirred for 2 hours. The insoluble material was removed from the reaction mixture by filtration and the filtrate was concentrated to dryness in vacuo. The resulting oil was dissolved in a mixture of trifluoroacetic acid (8 ml) and water (1 ml) and the solution was stirred at room temperature for 5 hours. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness. The resulting residue was purified by flash column chromatography on silica gel. The column was eluted with chloroform/methanol (20:1) to give 59 mg (42 %) of the title compound as white crystals. M.p. 163-166 °C.

IR (KBr)cm^{-1}: 1720, 1700, 1615, 1550, 1510.

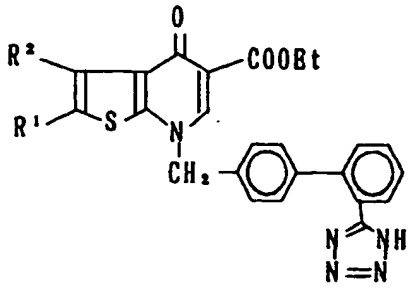
NMR ($CDCl_3$) δ : 1.14(3H, t, J=7.4Hz), 1.29(3H, t, J=7.0Hz), 2.03(3H, s), 2.63(2H, q, J=7.4, 15.0Hz), 4.23(2H, q, J=7.0, 14.2Hz), 5.45(2H, s), 7.13(2H, d, J=8.2Hz), 7.28(2H, d, J=8.2Hz), 7.5-7.7(4H, m), 8.74(1H, s), 9.66(1H, Bs).

Elemental Analysis for $C_{28}H_{26}N_6O_4S \cdot H_2O$

	C (%)	H (%)	N (%)
Calcd:	C, 59.99;	H, 5.03;	N, 14.99
Found:	C, 59.50;	H, 4.56;	N, 14.76

The following compounds (Working Examples 18- 20) as listed in Table 7 were prepared in the same manner as in Working Examples 12.

TABLE 7a



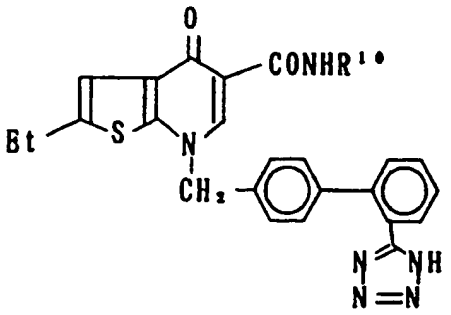
Working Example No.	R^1	R^2	MP.(°C)	Yield (%)
18	H	Me	167-170	30
19	Br	Me	227-231	77
20	CN	H	250-256	20

TABLE 7b

Working Example No.	NMR (d_6-DMSO) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
18	1.28(3H,t),2.47(3H,s),4.22(2H,q), 5.44(2H,s),6.92(1H,s),7.10(2H,d), 7.23(2H,d),7.5-7.7(4H,m),8.70(1H, s)	$C_{26}H_{21}N_5O_3S \cdot 0.2H_2O$ 63.20;4.54;14.74 63.00;4.37;14.80
19	1.29(3H,t),2.45(3H,s),4.23(2H,q), 5.43(2H,s),7.13(1H,d),7.27(2H,d), 7.5-7.8(4H,m),8.73(1H,s)	$C_{26}H_{20}BrN_5O_3S$ 54.55;3.66;12.72 54.82;3.63;12.83
20	1.29(3H,t),4.25(2H,q),5.52(2H,s), 7.13(2H,d),7.31(2H,d),7.5-7.8 (4H,m),8.25(1H,s),8.89(1H,s)	

The following compounds (Working Examples 21-36) were prepared in the same manner as in Working Example 12.

TABLE 8a



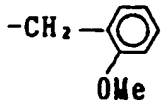
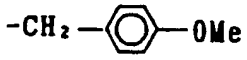
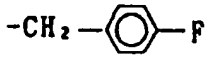
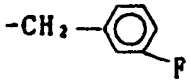
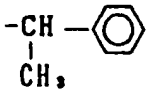
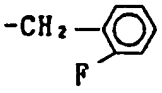
Working Example No.	R^{10}	MP (°C)	Yield (%)
21		134-148	42
22		223-225	67
23		202-204	54
24		powder	72
25		154-157	55
26		146-149	33

TABLE 8a

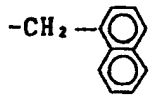
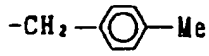
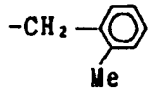
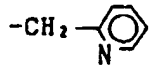
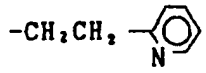
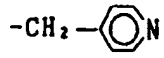
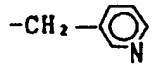
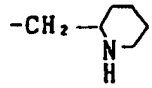
Working Example No.	R^{1a}	MP (°C)	Yield (%)
27		170-173	45
28		207-209	62
29		150-154	57
30		223-226	38
31		266-269	28
32		205-209	30
33		244-248	63
34		powder	72
35		247-248	33

TABLE 8a

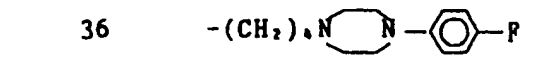
Working Example No.	R'°	MP (°C)	Yield (%)
36		188-190	36

TABLE 8b

Working Example No.	NMR (200MHz, $CDCl_3$) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
21	1.36(3H,t),2.89(2H,q),3.88(3H,s), 4.61(2H,d),5.12(2H,s),6.8-7.6 (12H,m),8.05-8.15(1H,m),8.30(1H,s)	
22	1.37(3H,t),2.89(2H,q),3.78(3H,s), 4.57(2H,s),5.20(2H,s),7.6-8.0 (13H,m),8.39(1H,s)	$C_{32}H_{28}N_6O_3S \cdot H_2O$ 64.63;5.08;14.13 64.92;4.74;13.99
23	1.38(3H,t),2.91(2H,q),4.60(2H,d), 5.18(2H,s),6.9-7.6(12H,m),8.1-8.2 (1H,m),8.29(1H,s),10.99(1H,brs)	$C_{31}H_{25}FN_6O_2S$ 65.94;4.46;14.88 65.94;4.45;14.71
24	1.37(3H,t),2.90(2H,q),4.61(2H,d), 5.16(2H,s),6.8-7.6(12H,m), 8.05-8.15(1H,m),8.34(1H,s)	
25	1.38(3H,t),1.58(3H,d),2.91(2H,q), 5.13(2H,s),5.22(1H,t),7.1-7.6 (13H,m),8.1-8.2(1H,m),8.20(1H,s), 11.05(1H,bs)	$C_{32}H_{28}N_6O_2S \cdot 0.5H_2O$ 67.47;5.13;14.75 67.64;4.99;14.52
26	1.37(3H,t),2.90(2H,q),4.67(2H,d), 5.16(2H,s),7.0-7.6(12H,m),8.05-8.15(1H,m),8.29(1H,s),10.97 (1H,brs)	$C_{31}H_{25}FN_6O_2S \cdot 1.5H_2O$ 62.93;4.77;14.20 63.02;4.30;14.03

TABLE 8b

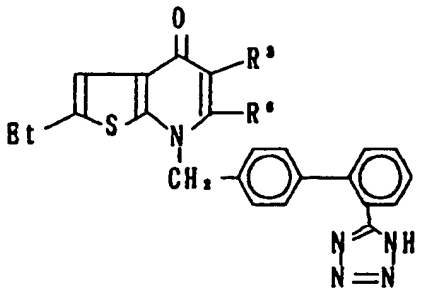
Working Example No.	NMR (200MHz) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
27	1.35(3H,t),2.86(2H,q),5.07(2H,s), 5.10(2H,s),7.1-7.9(14H,m),8.07 (2H,d),8.31(1H,brs),11.01(1H,brs) ;($CDCl_3$)	$C_{28}H_{28}N_6O_2S \cdot 0.5H_2O$ 69.40;4.83;13.87 69.40;4.65;13.64
28	1.37(3H,t),2.31(3H,s),2.90(2H,q), 4.57(2H,d),5.15(2H,s),7.0-7.6 (12H,m),8.0-8.2(1H,m),8.27(1H,brs) ;($CDCl_3$)	$C_{32}H_{28}N_6O_2S \cdot 0.5H_2O$ 67.47;5.13;14.75 67.54;5.14;14.57
29	1.37(3H,t),2.38(3H,s),2.90(2H,q), 4.61(2H,d),5.16(2H,s),7.0-7.6 (12H,m),8.0-8.2(1H,m),8.25(1H,brs) ;($CDCl_3$)	$C_{32}H_{28}N_6O_2S \cdot 0.2H_2O$ 68.11;5.07;14.89 68.01;4.85;14.94
30	1.32(3H,t),2.83(3H,q),4.65(2H,d), 5.35(2H,s),7.0-8.1(13H,m),9.34(1H, s),11.05(1H,t);($CDCl_3$)	$C_{30}H_{25}N_7O_2S \cdot HCl$ $0.5H_2O$ 60.75;4.59;16.53 60.83;4.29;16.36
31	1.24(3H,t),2.85(2H,q),3.01(2H,t), 3.6-3.8(2H,m),5.54(2H,s),7.0-7.8 (12H,m),8.5-8.6(1H,m),8.88(1H,s), 10.20(1H,t);(DMSO-d_6)	$C_{31}H_{27}N_7O_2S \cdot 0.5H_2O$ 65.25;4.95;17.18 65.27;4.79;17.13
32	1.38(3H,t),2.91(2H,q),4.90(2H,s), 5.34(2H,s),7.20(2H,d),7.28(2H,d), 7.37(1H,s),7.5-7.8(4H,m),7.96(2H, d),8.62(1H,s),8.78(2H,d);($CDCl_3$)	SIMS; 548(MH^+)
33	1.25(3H,t),2.85(2H,q),4.73(2H,d), 5.57(2H,s),7.12(2H,d),7.20(1H,s), 7.26(2H,d),7.5-8.9(8H,m),8.93(1H, s),10.71(1H,t);(DMSO-d_6)	$C_{30}H_{25}N_7O_2S \cdot HCl$ $\cdot 0.5H_2O$ 58.11;4.88;15.81 57.86;4.34;15.60
34	1.26(3H,t),1.3-1.9(6H,m),2.86(2H, q),3.0-3.7(5H,m),5.57(2H,s),7.14 (2H,d),7.21(1H,s),7.23(2H,d), 7.4-7.7(4H,m),8.6(1H,brs),8.91(1H, s),10.40(1H,t);(DMSO-d_6)	SIMS; 554(MH^{+1})

TABLE 8b

Working Example No.	NMR (200MHz) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
35	1.28(3H,t),1.78-1.94(2H,m),2.56-2.94(6H,m),3.09-3.27(4H,m),3.39-3.76(2H,m),5.53(2H,s),6.93-7.32(6H,m),7.43-7.66(4H,m),8.90(1H,s);(DMSO-d_6)	$C_{37}H_{37}FN_8O_2S \cdot 0.5H_2O$ 64.76;5.58;16.34 64.74;5.84;16.12
36	1.19(3H,t),1.25(3H,t),1.74-1.96(2H,m),2.66-3.56(16H,m),5.55(2H,s),6.90-7.31(9H,m),7.43-7.72(4H,m),8.92(1H,s);(DMSO-d_6)	$C_{38}H_{39}FN_8O_2S \cdot 3.5H_2O$ 60.54;6.15;14.86 60.31;5.96;14.85

The following compounds (Working Examples 37-45) were prepared in the same manner as in Working Example 12.

TABLE 9a



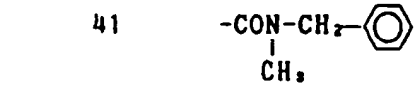
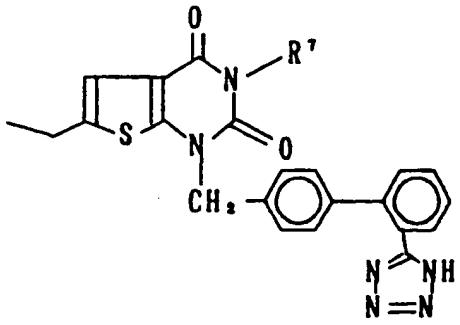
Working Example No.	R^3	R^6	MP (°C)	Yield (%)
37	$-CH_2OH$	H	>260 (dec.)	73
38	H	H	249-253	83
39	-CHO	H	powder	66
40	-CH=CHCOOtBu	H	powder	100
41		H	>190 (dec.)	88
42	$-CH_2OMe$	H	213-216	82
43	-COOH	CH_3	162-167	
44		CH_3	175-180	
45	-COOMe	$-CH_2COOMe$		

TABLE 9b

Working Example No.	NMR (200MHz) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
37	1.24(3H,t),2.79(2H,q),4.40(2H,s), 7.05(1H,s),7.11(2H,d),7.22(2H,d), 7.5-7.8(4H,m),7.98(1H,s);(DMSO-d_6)	$C_{24}H_{21}N_5O_2S \cdot 0.8H_2O$ 62.95;4.97;15.29 63.18;4.88;14.86
38	1.24(3H,t),2.80(2H,q),5.35(2H,s), 6.21(1H,d),7.07(1H,s),7.11(2H,d), 7.24(2H,d),7.4-7.8(4H,m), 8.08(1H,d);(DMSO-d_6)	$C_{23}H_{19}N_5OS \cdot H_2O$ 64.02;4.91;16.23 63.87;4.44;15.90
39	1.24(3H,t),2.82(2H,q),5.50(2H,s), 7.12(2H,d),7.20(1H,s),7.28(2H,d), 7.5-7.7(4H,m),8.69(1H,s),10.28(1H, s);(DMSO-d_6)	
40	1.25(3H,t),1.37(9H,s),2.80(2H,q), 5.35(2H,s),6.93(1H,d),7.1-7.9(10H, m),8.55(1H,s);(DMSO-d_6)	
41	1.19(3H,t),1.21(3H,t),2.69(2H,q), 2.96(3H,s),4.58(2H,s),4.79(2H,s), 5.38(2H,s),6.7-7.6(13H,m),7.9-8.0 (1H,m),8.6(1H,brs);($CDCl_3$)	$C_{32}H_{28}N_6O_2S \cdot 0.5H_2O$ 67.47;5.13;14.75 67.64;4.99;14.52
42	1.21(3H,t),2.69(2H,q),3.44(3H,s), 4.09(2H,s),5.21(2H,s), 6.8-7.9(10H,m);($CDCl_3$)	$C_{25}H_{23}N_5O_2S \cdot 0.7H_2O$ 63.87;5.23;14.90 64.00;4.99;14.69
43	1.27(3H,t),2.88(2H,q),2.95(3H,s), 5.68(2H,s),7.11(4H,s),7.29(1H,s), 7.5-7.8(4H,m);(DMSO-d_6)	$C_{25}H_{21}N_5O_3S \cdot 0.5H_2O$ 62.49;4.61;14.57 62.28;4.36;14.39
44	1.39(3H,t),2.75(3H,s),2.99(2H,q), 5.85(2H,s),7.1-7.8(14H,m);(CD_3OD)	SIMS; 547(MH^+)
45	1.32(3H,t),2.86(2H,q),3.66(3H,s), 3.88(3H,s),3.94(2H,s),5.55(2H,s), 6.98(2H,d),7.13(2H,d),7.22(1H,s) 7.4-7.7(4H,m);(CD_3OD)	SIMS; 544(MH^+)

The following compounds (Working Examples 46-53) were prepared in the same manner as in Working Example 2.

TABLE 10a



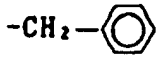
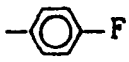
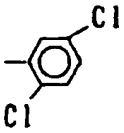
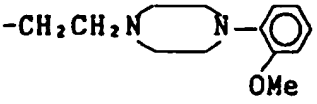
Working Example No.	R^7	MP (°C)	Yield (%)
46	Bu	127-130	32
47		202-205	65
48	Et	210-212	59
49		246-250	70
50		powder	31
51		207-221	57
52	$-CH_2COOEt$	167-169	44
53		powder	77

TABLE 10b

Working Example No.	^{1}H-NMR ($CDCl_3$) δ	E. Anal. (Calcd/Found) C(%), H(%), O(%)
46	0.92(3H,t),1.30(3H,t),1.2-1.5(2H,m),1.5-1.8(2H,m),2.77(2H,q),4.01(2H,t),5.15(2H,s),7.00(1H,s),7.23(2H,d),7.42(2H,d),7.5-7.7(3H,m),8.1-8.2(1H,m)	$C_{24}H_{26}N_6O_2S$ 64.18;5.39;17.27 64.00;5.51;17.18
47	1.21(3H,t),2.75(2H,q),5.12(2H,s),5.15(2H,s),7.02(1H,s),7.09(2H,d),7.2-7.8(11H,m)	$C_{24}H_{24}N_6O_2S \cdot 0.4H_2O$ 65.99;4.74;15.92 66.17;4.91;15.63
48	1.25(3H,t),1.30(3H,t),2.78(2H,q),4.08(2H,q),5.16(2H,s),7.01(1H,s),7.23(2H,d),7.43(2H,d),7.5-7.7(3H,m),8.1-8.2(1H,m)	$C_{24}H_{22}N_6O_2S \cdot 0.5H_2O$ 61.65;4.96;17.97 61.70;4.83;17.80
49	1.32(3H,t),2.81(2H,q),5.14(2H,s),7.06(1H,s),7.1-7.8(12H,m)	$C_{24}H_{21}FN_6O_2S$ 64.11;4.04;16.02 63.82;3.97;15.77
50	1.33(3H,t),2.81(2H,q),5.20(2H,q),7.07(1H,s),7.2-8.2(11H,m)	$C_{24}H_{20}N_6O_2SCl_2 \cdot 0.6H_2O$ 57.36;3.64;14.33 57.74;3.75;13.75
51	1.29(3H,t),1.2-2.6(10H,m),2.76(2H,q),4.7-5.0(1H,m),5.13(2H,s),6.99(1H,s),7.24(2H,d),7.42(2H,d),7.5-7.7(3H,m),8.1-8.2(1H,m)	$C_{24}H_{28}N_6O_2S \cdot 0.4H_2O$ 64.69;5.58;16.17 64.81;5.50;15.95
52	1.29(3H,t),1.31(3H,t),2.79(2H,q),4.23(2H,q),4.80(2H,s),5.17(2H,s),7.03(1H,s),7.22(2H,d),7.4-7.7(5H,m),8.1-8.2(1H,m)	$C_{24}H_{24}N_6O_4S$ 60.45;4.68;16.27 60.33;4.59;16.17
53	1.36(3H,t),2.84(2H,q),2.8-3.6(8H,m),3.83(3H,s),4.2-4.5(4H,m),4.97(2H,s),6.8-7.2(7H,m),7.4-7.6(5H,m),7.94(1H,d)	$C_{31}H_{36}N_8O_3S \cdot CF_3COOH \cdot 2.5H_2O$ 55.01;5.24;13.87 54.51;4.74;13.45

Pharmaceutical Examples

The compounds (I) of the present invention are employed, for example, when used as agents for treating circulatory system diseases such as hypertension, heart diseases, strokes and the like, in the following formulations.

1. Capsule

(1)	Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno-[2,3-b]pyridine-5-carboxylate	10 mg
(2)	Lactose	90 mg
(3)	Microcrystalline cellulose	70 mg
(4)	Magnesium stearate	10 mg
	One capsule	180 mg

The ingredients (1), (2), and (3) and a half of the ingredient (4) were blended together and granulated. To this mixture was added the remaining half of the ingredient (4) and distributed into gelatine capsules.

2. Tablet

(1)	Ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno-[2,3-b]pyridine-5-carboxylate	10 mg
(2)	Lactose	35 mg
(3)	Maize starch	150 mg
(4)	Microcrystalline cellulose	30 mg
(5)	Magnesium stearate	5 mg
	One tablet	230 mg

Two third each of the ingredients (1), (2), (3) and (4) and a half of the ingredient (5) were blended together and granulated. To these granules were added the remaining ingredients (4) and (5) and then compressed to form tablets.

3. Injection

(1)	2-Ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-thieno[2,3-b]pyridine-5-carboxylic acid · sodium salt	10 mg
(2)	Inositol	100 mg
(3)	Benzyl alcohol	20 mg
	One ampule	130 mg

The ingredients (1), (2) and (3) were dissolved in distilled water for injection to a total volume of two ml and distributed into ampules. Total processes were carried out under sterile conditions.

Experimental Example 1

Inhibition of binding of angiotensin-II to angiotensin receptor

[Method]

An experiment of inhibition on the binding of angiotensin-II (A-II) to A-II-receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685-696 (1978)]. An A-II-receptor was prepared from the membrane fraction of bovine adrenal cortex.

The compound of the present invention (10^{-9}M to 3 × 10^{-5}M) and ^{125}I-A-II (1.85 kBq/50 μ l) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-A-II were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-A-II bound to the receptor was measured.

[Results]

The results relating to the compounds of the present invention are shown in Table 11.

Experimental Example 2

Inhibitory effect of the compound of the present invention on pressor action of A-II

[Method]

Jcl : SD rats (9 week old, male) were used. On the day previous to the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed to access freely to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means of polygraph. Before administration of the drug, the pressor action due to intravenous administration of A-II (100 ng/kg) as the control was measured. The drugs were orally administered, and then, at each point of the measurement, A-II was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on A-II-induced pressor action was evaluated.

[Results]

The results relating to the compounds of the present invention are shown in Table 11.

TABLE 11

Working Example No.	Radio Receptor Assay (% Inhibition) 10^{-7}(M)	10^{-6}(M)	IC_{50}(μM)	Pressor Response (30 mg/Kg, p.o.)
2	69	94	0.05	NT**
3	51	81	0.07	NT
4	34	68	0.20	NT
5	56	88	0.05	NT
6	48	83	0.09	NT
7	40	82	0.17	NT
8	81	94	0.01	NT
10	51	86	0.04	+**
11	42	83	0.21	NT
12	57	89	0.06	++
13	78	93	0.02	NT
14	45	87	0.13	NT
15	62	90	0.05	NT
16	47	85	0.12	++
20	22	56	0.67	NT
21	36	71	0.25	++
23	40	81	0.17	++
24	37	82	0.19	++

TABLE 11 (continued)

Working Example No.	Radio Receptor Assay (% Inhibition) 10^{-7}(M)	10^{-6}(M)	IC_{50}(μM)	Pressor Response (30 mg/Kg, p.o.)
25	8	55	0.78	++
26	35	81	0.21	++
28	36	78	0.22	+
29	47	86	0.12	++
30	70	93	0.02	++

*a : NT , not tested.

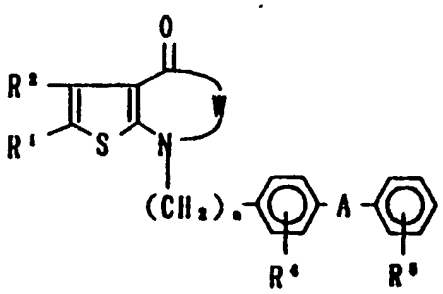
*b : (% Inhibition), ++ ≧ 70 % > + ≧ 50 %.

It is understood that the preceding representative examples may be varied within the scope of the present invention by one skilled in the art to achieve essentially the same results.

As many widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

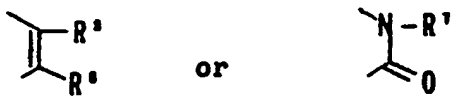
Claims

1. A compound of the formula:



(I)

wherein W is

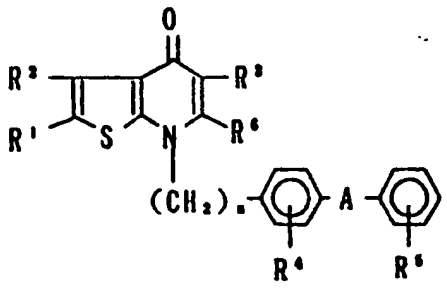


R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;

R^3 is hydrogen, optionally substituted alkyl or alkenyl, or -COD wherein D is hydrogen, alkoxy, hydroxy, halogen, or optionally substituted amino;

R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^6 is hydrogen or optionally substituted alkyl or alkenyl;
R^7 is a hydrocarbon residue which may be substituted;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2;
and a pharmaceutically acceptable salt thereof.

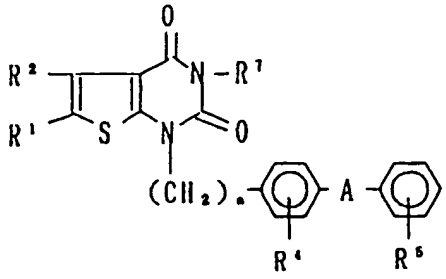
2. A compound according to claim 1, which is a compound of the formula (Ia):



(Ia)

wherein R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^3 is hydrogen, formyl, optionally substituted alkyl or alkenyl, or -COD wherein D is alkoxy, hydroxy, halogen, or optionally substituted amino;
R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^6 is hydrogen or optionally substituted alkyl or alkenyl;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2;
and a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, which is a compound of the formula (Ib):



(Ib)

wherein R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^7 is a hydrocarbon residue which may be substituted;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and
n is an integer of 1 or 2;
and a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein the acylamino group is a group having the formula: R^8CONH-wherein R^8 is hydrogen or a hydrocarbon residue which may be substituted.

5. A compound according to claim 4, wherein the hydrocarbon residue is lower alkyl of 1 to about 8 carbon atoms, lower alkenyl of 2 to about 8 carbon atoms, lower alkynyl of 2 to about 8 carbon atoms, an alicyclic hydrocarbon residue of 3 to about 8 carbon atoms, or an aromatic hydrocarbon residue of about 6 to 12 carbon atoms.

6. A compound according to claim 1, wherein the hydrocarbon residue is lower alkyl of 1 to about 8 carbon atoms, lower alkenyl of 2 to about 8 carbon atoms, lower alkynyl of 2 to about 8 carbon atoms, an alicyclic hydrocarbon residue of 3 to about 8 carbon atoms, or an aromatic hydrocarbon residue of about 6 to 12 carbon atoms.

7. A compound according to claim 1, wherein said hydrocarbon residue may be optionally substituted with hydroxyl, lower (C_{1-4}) alkoxy, lower (C_{1-4}) alkyl, halogen, nitro, optionally substituted amino, acyloxy, optionally substituted phenyl, or a group having the formula: -COD' wherein D' is hydroxy, lower (C_{1-4}) alkoxy, or optionally substituted amino.

8. A compound according to claim 7, wherein said optionally substituted amino is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, N-phenylpiperazino, or N-(m-methoxy)phenylpiperazino.

9. A compound according to claim 7, wherein said acyloxy is lower (C_{1-4}) alkanoyloxy or benzoyloxy.

10. A compound according to claim 7, wherein said phenyl may be optionally substituted with halogen, nitro, lower (C_{1-4}) alkoxy, or lower (C_{1-4}) alkyl.

11. A compound according to claim 7, wherein said D' is amino, methylamino, dimethylamino, phenylamino, benzylamino, morpholino, piperidino, piperazino, or N-phenylpiperazino.

12. A compound according to claim 1, wherein said optionally substituted alkyl or alkenyl group is lower alkyl of 1 to about 8 carbon atoms or lower alkenyl of 2 to about 8 carbon atoms which may be straight or branched and may be optionally substituted with hydroxyl, optionally substituted amino, halogen, lower (C_{1-4}) alkoxy, or -COD" wherein D" is lower (C_{1-4}) alkoxy, hydroxy, halogen, or optionally substituted amino.

13. A compound according to claim 1, wherein said D is amino, N-lower (C_{1-4}) alkyl amino, N,N-dilower (C_{1-4}) alkyl amino, N-arylamino, N-aralkylamino, N-heteroarylamino, N-heteroaralkylamino, or alicyclic amino, wherein said alkyl, aryl and heteroaryl groups may be optionally substituted with alkyl, hydroxyl, optionally substituted amino, halogen, nitro, lower (C_{1-4}) alkoxy, or alicyclic amino.

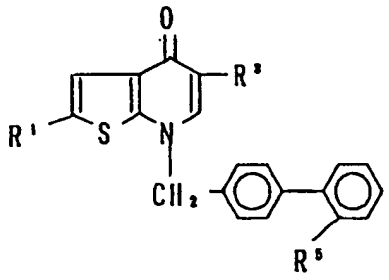
14. A compound according to claim 1, wherein said R^5 is carboxyl, lower (C_{1-4}) alkoxycarbonyl, cyano, tetrazolyl, trifluoromethanesulfonic amide, phosphoric acid, or sulfonic acid.

15. A compound according to claim 14, wherein said R^5 is tetrazolyl.

16. A compound according to claim 14, wherein said R^5 is in the ortho position.

17. A compound according to claim 1, wherein said A is lower (C_{1-4}) alkylene, -C(=O)-, -O-, -S-, -NH-, -C(=O)-NH-, $-O-CH_2-$, $-S-CH_2-$, or -CH=CH-.

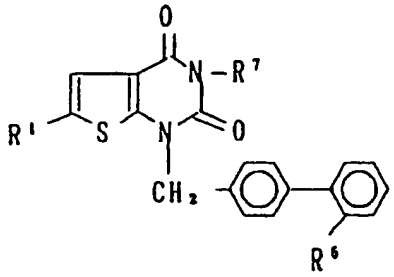
18. A compound according to claim 1, which is a compound of the formula (Ia'):



(Ia')

wherein R^1 is lower (C_{1-8}) alkyl; R^3 is hydrogen, optionally substituted lower (C_{1-8}) alkyl or COD wherein D is hydrogen, lower (C_{1-4}) alkoxy, hydroxy, or optionally substituted amino; and R^5 is carboxyl or tetrazolyl;
or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 1, which is a compound of the formula (Ib'):



(Ib')

wherein R^1 is lower (C_{1-8}) alkyl; R^7 is hydrogen, lower (C_{1-8}) alkyl which may be optionally substituted with optionally substituted aryl, optionally substituted amino or COD wherein D is lower (C_{1-4}) alkoxy, hydroxy, or optionally substituted amino, (C_{3-8}) cycloalkyl or optionally substituted aryl; and R^5 is carboxyl or tetrazolyl;
or a pharmaceutically acceptable salt thereof.

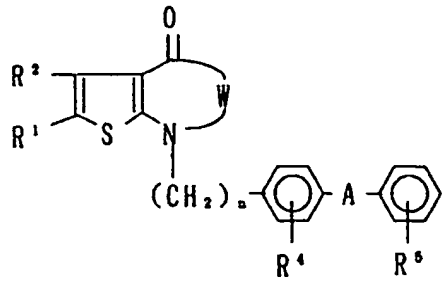
20. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of ethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]-pyridine-5-carboxylate, 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine-5-carboxylic acid, methoxyethyl 2-ethyl-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]-pyridine-5-carboxylate, 2-ethyl-5-(N-benzylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine, 2-ethyl-5-(N-phenylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxothieno[2,3-b]pyridine, and 2-ethyl-5-(N-2-pyridylmethylcarbamoyl)-7-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4-oxo-thieno[2,3-b]pyridine.

21. A compound according to claim 19, wherein R^1 is ethyl, R^5 is 1H-tetrazol-5-yl and R^7 is butyl, benzyl, ethyl, p-fluorophenyl, 2,5-dichlorophenyl, cyclohexyl, ethoxycarbonylmethyl, or 2-[4-(o-methoxyphenyl)-piperazino]ethyl.

22. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutical acceptable carrier, excipient or diluent.

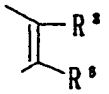
23. A use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for antagonizing angiotensin II.

24. A method for producing a compound of the formula (I):

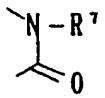


(I)

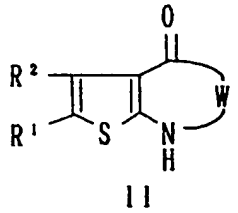
wherein W is



or

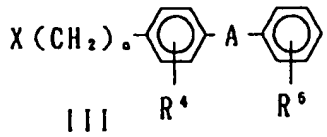


R^1 and R^2 which may be same or different, are each independently hydrogen, halogen, cyano, nitro, acylamino, or a hydrocarbon residue which may be substituted;
R^3 is hydrogen, optionally substituted alkyl or alkenyl, or -COD wherein D is hydrogen, alkoxy, hydroxy, halogen, or optionally substituted amino;
R^4 is hydrogen, halogen or nitro;
R^5 is a residue capable of forming an anion or a residue convertible into an anion;
R^6 is hydrogen or optionally substituted alkyl or alkenyl;
R^7 is a hydrocarbon residue which may be substituted;
A is a direct bond or a spacer having atomic length of two or less between the phenylene group and the phenyl group; and n is an integer of 1 or 2;
or a pharmaceutically acceptable salt thereof,
which comprises
reacting a compound of the formula (II):



II

wherein R^1, R^2, and W have the above-defined meanings, with a compound of the formula (III):



III

wherein R^4, R^5, A and n have the above-defined meanings, and X is halogen,

and, (i) if desired, converting a compound of the formula (I) wherein R^5 is cyano or protected tetrazolyl, and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, into a compound of the formula (I) wherein R^5 is tetrazolyl and R^1, R^2, R^4, R^5, A, W and n have the above-defined meanings, (ii) if desired, converting a compound of the formula (I) wherein $-R^3$ is lower (C_{1-4}) alkoxycarbonyl or halogenocarbonyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is carboxyl, or optionally substituted carbamoyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, or (iii) if desired, converting a compound of the formula (I) wherein $-R^3$ is carboxyl, and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, into a compound of the formula (I) wherein R^3 is halogenocarbonyl and R^1, R^2, R^4, R^5, R^6, A and n have the above-defined meanings, and, if desired, converting a compound of the formula (I) into a pharmaceutically acceptable salt thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 10 2513

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, 1988, pages 1786 - 1793; R.K. RUSSELL et al.: "Thiophene Systems. 9. Thienopyrimidinedione Derivatives as Potential Antihypertensive Agents." * page 1788, table III *	1,3,23	C 07 D 495/04 A 61 K 31/435 // (C 07 D 495/04 C 07 D C 07 D 333:00 C 07 D 221:00)
A	US-A-4 670 560 (J.B. PRESS ET AL.) * column 8, lines 6 - 37; claim 1 * * examples 47, 48 *	1,3,22,23	(C 07 D 495/04 C 07 D C 07 D 333:00
A	US-A-4 835 157 (J.B. PRESS ET AL.) * claims 1, 19, 24, 29 *	1,3,22,23	C 07 D 239:00)
A	CHEMICAL ABSTRACTS, vol. 99, no. 3, 18 July 1983 Columbus, Ohio, USA R. BOEHM et al.: "Thieno compounds. Part 1. Phase transfer-catalyzed alkylation of thieno[2,3-d]pyrimidin-4[3H]-ones or -2,4-diones" page 616; ref. no. 22419Q & Pharmazie 1983, 38[2], 135-6 * abstract *	1,3,24	
A	US-A-4 880 804 (D.J. CARINI ET AL.) * claims 1, 9 *	1,22,23	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	EP-A-0 323 841 (E.I. DU PONT DE NEMOURS AND CO.) * page 2, lines 23 - 31; claims 1, 10, 14 *	1,22-24	C 07 D 495/00
A,P	EP-A-0 400 835 (MERCK AND CO., INC.) * page 12, reaction scheme 1; page 25, lines 4-7; abstract *	1,22-24	
A,D	HYPERTENSION, vol. 13, 1989, Dallas, Tex., US, pages 489 - 497; P.C. WONG et al.: "Nonpeptide Angiotensin II Receptor Antagonists. IV. EXP6155 and EXP6803"	22,23	

-/-

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
Berlin	05 June 91	HASS C V F

CATEGORY OF CITED DOCUMENTS

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- Y: particularly relevant if combined with another document of the same catagory
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- D: document cited in the application
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& : member of the same patent family, corresponding document

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 247, no. 1, October 1988, pages 1 - 7; P.C. WONG et al.: "Nonpeptide Angiotensin II Receptor Antagonists. I. Pharmacological Characterization of 2-n-Butyl-4-chloro-1-[2-chlorobenzyl]..."	22,23	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
Berlin	05 June 91	HASS C V F

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